BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JUNE 1945

MASS SULFADIAZINE PROPHYLAXIS OF RESPIRATORY DISEASES IN THE U. S. NAVY*

ALVIN F. COBURN

Commander (MC) USNR

INTRODUCTION

THE delicate balance which exists between respiratory pathogens and the human host is frequently disturbed in times of war. A balance unfavorable to military personnel is produced in at least three ways: (a) by the spreading of virus infections of the respiratory tract; (b) by the introduction of bacterial strains with great pathogenicity; and (c) by the dissemination of these strains among susceptible recruits. This sequence occurred in World War I. Outbreaks of measles were common at training camps and influenza reached pandemic proportions. Following these virus diseases, hemolytic streptococcus acquired great pathogenicity. In 1918-19 this bacterium accounted for at least 242,000 casualties (exclusive of pneumonia and probable streptococcal diseases) in the armed forces. Approximately 7 per cent of the mean annual strength of the armed forces was hospitalized with streptococcal infections; approximately 56,000 men were crippled with rheumatic fever or acute rheumatism; the mortality rate from streptococcal infection

* Presented before The New York Academy of Medicine, October 10, 1944, in the Seventeenth Graduate Fortnight.

was high. It is now well known that deaths from respiratory pathogens during World War I exceeded the fatalities of trench warfare.

At the onset of World War II, military medicine had equipped itself to prevent fatalities from respiratory infections. Nevertheless, hemolytic streptococcus accounted for over 47,000 infections in the U. S. Navy during the first year of the war. Most of these were minor casualties; however, there was an impressive list of disabling streptococcal complications: 5,231 otitis, 2,736 sinusitis, 1,002 acute arthritis, 869 rheumatic fever, 876 valvular heart disease, and 171 mastoiditis. The low mortality rate associated with the advent of sulfonamides obscured the fact that at least 2,700,000 man-days were lost to the Navy during the first year of World War II from proved or probable streptococcal infections. Nevertheless, in 1943 the morbidity rate from scarlet fever reached a level far higher than ever recorded in the history of the U. S. Navy.

It was anticipated that a marked increase in the incidence and severity of streptococcal infections would occur in the U. S. Navy during 1943 because conditions occasioned by rapidly expanded training programs were comparable to those created in experimental epidemiology. It was believed that under existing conditions in training camps, hemolytic streptococcus would manifest increased infectivity, would develop variants endowed with great pathogenicity and would create incalculable damage to Navy personnel. This sequence of events became manifest in 1943. During the summer months of 1943 the activity of meningococcus and pneumococcus subsided. However, at one Naval activity hemolytic streptococcus maintained its pathogenicity and late in 1943 this bacterium exhibited increased virulence. Furthermore, strains of this bacterium, identified serologically as types 17, 1, and 19, maintained their pathogenicity when transplanted by carriers to other geographical environments and even initiated streptococcal epidemics at Naval activities situated in southern states.

Factors in the Pathogenesis of Respiratory Epidemics at Naval Training Stations

Five conditions favoring the development of respiratory epidemics were satisfied at several large Naval training stations in World War II. Fresh, highly susceptible recruits were introduced almost daily; there was a high rate of change in population during the program for rapid

training; overcrowding and the congestion of large numbers of men in sleeping quarters occurred; outbreaks of influenza or measles developed at large training centers; most of the training stations were seeded with strains of respiratory pathogens that manifested great communicability.

Other less obvious factors, which varied from station to station, were also operative. At some, temperatures were high indoors and extremely low outdoors during the winter months. At others, dust storms presented a serious local problem during the summer months. Rapid fluctuations in outdoor temperatures, rain, snow, fog, and other climatic states were variables at each activity. Many of these conditions, not subject to appraisal, were unfavorable to the normal, physiological responses of the host and, therefore, favorable to the invasion of bacterial respiratory pathogens.

Conditions which facilitate the transmission of respiratory pathogens during recruit training are now being recognized: (1) The contamination of food, which may cause explosive outbreaks of throat infections, is always a potential danger. (2) The direct transmission of respiratory pathogens from infected individuals during the incubation and convalescent states is accelerated by overcrowding and billeting in times of war. The use of double-deck bunks permits the direct transmission of large innocula of bacteria from man to man. (3) The possibility of insufflation of infected particulate matter occurs with intensive recruit training in swimming. One man plunges into the water of a pool and contaminates it with purulent exudate from the nasal sinuses or the respiratory tract. This material, uninfluenced by short exposure to chlorine, may be forced under pressure into the ears, sinuses or respiratory passages of the recruits who follow in quick succession. The chlorination of swimming pool water may give little protection under these conditions, although affording a satisfactory bacterial count on analysis. Furthermore, chlorine acts as an irritant to the mucous membranes of many individuals. This may be one of the several factors inherent in swimming, which lower the resistance of mucous membranes and increase susceptibility to the invasion of bacterial pathogens already harbored. (4) Indirect transmission of airborne respiratory pathogens is tremendously accelerated by rapidly expanding training programs. "Convalescent carriers" of hemolytic streptococcus are, per force, barracked in recruit camps and contaminate decks and blankets. These barracks are filled with new trainees as

soon as billets become empty. Dust and blanket lint containing millions of organisms are disseminated with each cleaning of the decks and manipulation of blankets. The rapid turnover of recruits and the failure to recognize the importance of dust control measures permit ideal conditions for the inhalation of small numbers of respiratory pathogens by large numbers of trainees. If these trainees be recruits, their susceptibility is further enhanced by a coincident lowering of resistance associated with acclimatization, changes in living conditions, and reactions to active immunization against tetanus, smallpox, yellow fever, typhus fever, and enteric infections. (5) The indirect transmission of air-borne respiratory bacterial pathogens is further accelerated by the passage, directly or indirectly, of certain viruses. Measles and influenza are air-borne infections disseminated with great facility in crowded barracks. Irrespective of whether an individual recruit contracts or escapes these virus infections, there can be no doubt that one of the final effects of virus activity in a Naval training station is increased pathogenicity of the prevalent strains of hemolytic streptococcus. With increased pathogenicity of this bacterium, the morbidity rate rises. This rise is followed by increasing dissemination, which facilitates the epidemic process.

Theoretically, it is possible to break this process of spreading contagion because methods are available to control each factor in the initiation and perpetuation of a respiratory epidemic. Medical science has almost eliminated the explosive outbreaks caused by the ingestion of food infected wtih hemolytic streptococcus. Careful screening of convalescents before their return to duty and elimination of double-deck bunks will reduce the incidence of "return cases" who have been infected directly by the inhalation of infected droplets. The institution of technique for dust control, such as oiling of the blankets and decks with bactericidal emulsions, will reduce the incidence of indirectly transmitted air-borne infections. The cessation of instruction in swimming pools will eliminate infections caused by insufflation. The suppression of influenza by active immunization and measles by passive immunization may remove the most important virus factors. The protection of a recruit from infection during the first three weeks of "boot" training, when he is being acclimatized and actively immunized, will increase his resistance at the time of maximum exposure to hemolytic streptococcus.

Practically, it is impossible to control all of these factors while conducting a rapidly expanding training program. The future will undoubtedly see Preventive Medicine apply the necessary control measures. The present must accept the fact that the dissemination and inhalation of air-borne respiratory pathogens is not yet controlled by Naval sanitation. The medical officer cannot yet prevent the seeding of microörganisms, the rooting of these pathogens in the floor dust, the growth of these infectious agents among his men, the branching of this epidemic process to other men in his barracks, but he can now check the fruition of an epidemic process by preventing implantation of respiratory pathogens in susceptible recruits. It was for this purpose that the heroic measure of mass chemoprophylaxis was employed by the U. S. Navy.

A Program for the Control of Streptococcal Infections

The Navy's enormous loss of man-days to Streptococcus haemolyticus was only one of the compelling reasons for instituting a Streptococcal Control Program. For military and civilian welfare it became essential to prevent the dissemination of respiratory pathogens among Naval personnel, to prevent the induction of rheumatic fever with the development of incapacitating heart disease, to prevent the invasion of streptococcus into deep tissues with the formation of suppurative lesions and to prevent the spreading of this highly virulent organism from one Naval activity to another. To attain these objectives, a long-term Streptococcal Control Program was instituted in November 1943.

The first objective of this program was to check the rapidly rising respiratory infection morbidity rates in the winter of 1944 by preventing the implantation of pathogenic bacteria in the nasopharynx. Continuous chemoprophylaxis was selected as the most promising control measure. To test the applicability of chemoprophylaxis under controlled conditions and to determine a standard prophylactic dose of sulfadiazine, programs were designed for five large northern training stations with high respiratory disease rates. Groups of trainees were then selected to receive sulfadiazine prophylaxis and comparable groups to serve as untreated controls. At each station these groups were placed under the supervision of an Epidemiology Unit.

On December 1, 1943 this controlled program was initiated at five training stations. Data on the incidence of respiratory infections in the

"treated" and control groups were collected for three months. With the accumulation of these data, the effectiveness of mass prophylaxis was manifest. It was then decided to extend the program to three other Naval activities experiencing a high incidence of streptococcal infections and to discontinue the use of untreated controls in the five Naval activities at which the sulfadiazine program was already in operation. Continuous mass prophylaxis was accordingly extended to about fifty camps of eight Naval activities, and this program was continued throughout the spring months of 1944.

Administration

Camps with high streptococcal morbidity rates, or half of each of these camps, were selected as the groups to receive chemoprophylaxis. Similar camps, or the other half of a camp, served as controls. Accurate daily records were kept of all patients with respiratory diseases seen at sick call or admitted to dispensary sick bay or hospital. In addition, an epidemiologist made daily visits to each recruit unit dispensary and to the Naval hospital. Clinical diagnoses on all respiratory diseases were checked and corrected. Throat cultures were made on all patients with frank or probable streptococcal diseases, including scarlet fever, tonsillitis, pharyngitis, erysipelas, otitis media, mastoiditis and sinusitis.

Blood samples were obtained for the determination of blood sulfadiazine levels from cases with frank or probable streptococcal or meningococcal diseases in the treated areas. Beta hemolytic streptococci recovered from the throat flora were isolated in pure culture, transferred to blood agar slants and shipped to the Streptococcus Typing Laboratory at the National Naval Medical Center, Bethesda, Maryland, for grouping, typing, and sulfonamide-fastness studies.

Clinical records were begun several weeks prior to the institution of prophylaxis to establish a preliminary base line. The dispensing of sulfadiazine tablets was placed under the direct personal supervision of the company commander and company clerk of each company. A "check-off list" insured that each man received his dose, and he was required to swallow this 1 gram with water in the presence of the company commander. No one was excused from taking the drug unless possessing a certificate from the medical officer of his unit indicating that he was sensitive to sulfonamide.

Results

The effectiveness of chemoprophylaxis in the control of streptococcal respiratory infections became apparent at the end of the first week. After two weeks, the incidence of rheumatic fever began to decline and then fell progressively. By the end of one month the incidence of scarlet fever, tonsillitis, and rheumatic fever reached a relatively low level in each group receiving chemoprophylaxis. It was also apparent early in this program that sulfadiazine prophylaxis had no effect on the incidence of influenza, measles, atypical pneumonia and other diseases believed to be caused by filtrable viruses.

A. Effectiveness of Chemoprophylaxis in the Control of Respiratory Diseases:

Continuous chemoprophylaxis with 1 gram of sulfadiazine daily was highly effective in preventing bacterial infections of the respiratory tract of susceptible recruits. This was evidenced in the following ways:

1. *Effect on Throat Flora:* Throat culture studies were made on recruits upon arrival at a Naval training station and four weeks later. It was observed that men who did not receive chemoprophylaxis acquired hemolytic streptococcus in their throat flora. The carrier rate rose throughout training in control groups. However, in groups receiving chemoprophylaxis the carrier rate of hemolytic streptococcus either remained at the level observed on arrival or fell to a moderately lower level. This is illustrated in Chart 1.

2. *Effect on Total Respiratory Infection:* The incidence of respiratory infections was lower in all groups receiving chemoprophylaxis than in the controls. This difference in morbidity rates was due largely to the effectiveness of sulfadiazine in preventing streptococcal infections. This is illustrated by observations made at a Naval training center where measles and influenza (catarrhal fever) were prevalent and bacterial respiratory pathogens disseminated throughout all areas of this training activity. Chart 2 shows the effectiveness of chemoprophylaxis under conditions least favorable to the host and most favorable to the spread of respiratory infections.

3. *Effect on the Incidence of Respiratory Symptoms:* Men in groups receiving chemoprophylaxis had fewer respiratory symptoms than men in control groups. At some stations the reduction in sick call

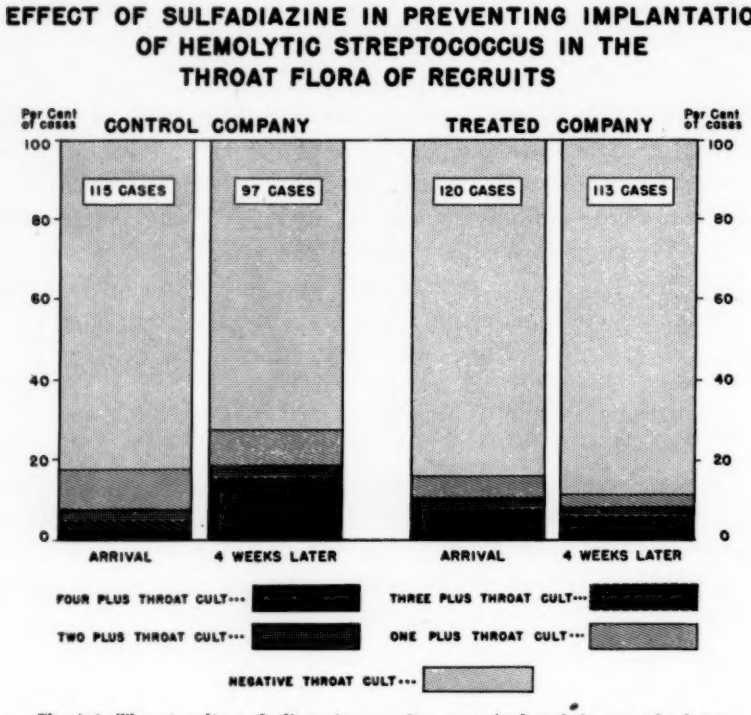

Chart 1. Throat culture findings in recruits on arrival and four weeks later.

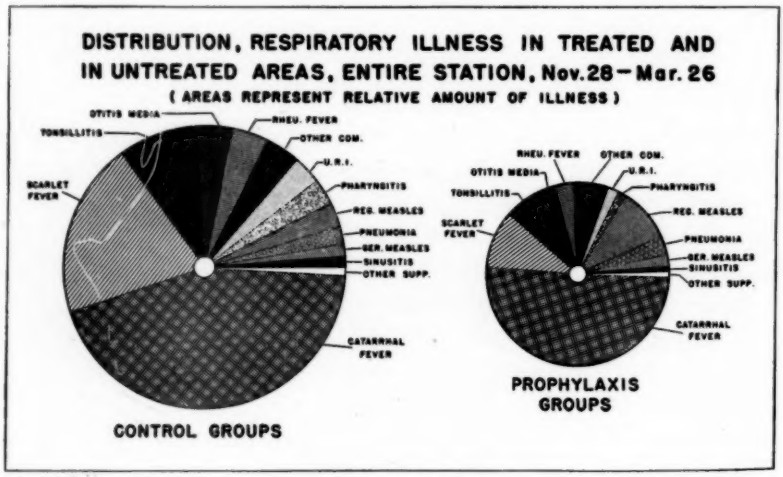

Chart 2 Respiratory diseases on a station of 50,000 men, about half of whom received chemoprophylaxis.

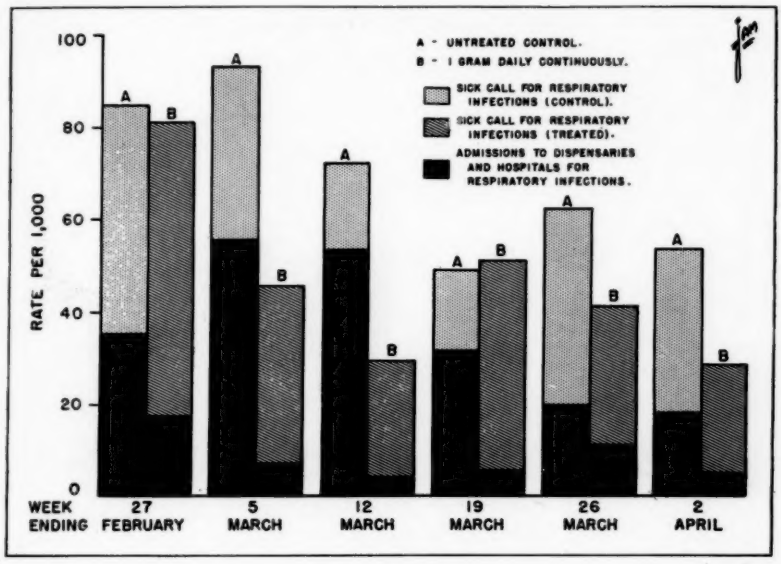

Chart 3. Sick call and admission rates for respiratory symptoms in a camp of 5,000 men, half of whom received chemoprophylaxis.

visits for respiratory symptoms was 50 per cent in groups receiving chemoprophylaxis. At other stations the reduction was less striking. This variation was probably associated with the relative prevalence of virus diseases. Observations presented in Chart 3 indicate what may be expected from chemoprophylaxis during the winter months when both virus and bacterial respiratory pathogens are active in a camp of 5,000 men.

4. *Effect on the Incidence of Severe Respiratory Diseases:* One of the most striking effects of chemoprophylaxis has been the prevention of respiratory diseases which require hospital care. This was indicated in Chart 3 and is more striking in Chart 4. Chart 4 shows the admission rates to a Naval hospital from a training center where 15,000 recruits received chemoprophylaxis and 10,000 recruits were observed as controls.

5. *Effect on the Sequelae of Influenza:* Although chemoprophylaxis does not lower the incidence of influenza, morbidity rates for respiratory infections following influenza were lower in groups receiving sulfadiazine than in control groups. This is illustrated in Chart 5. This

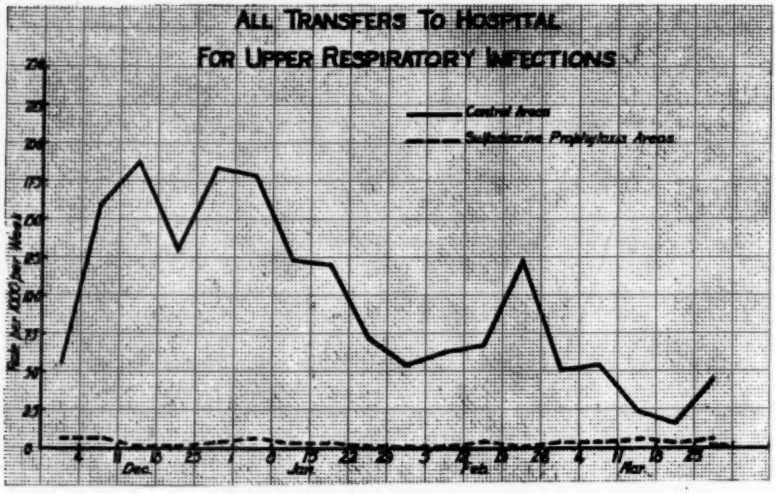

Chart 4. Hospital admission for upper respiratory diseases on a station where 15,000 recruits received chemoprophylaxis and 10,000 recruits served as untreated controls.

chart shows the morbidity rates in two battalions at one camp. Both experienced a severe outbreak of influenza in November 1943. Following this outbreak, the incidence of respiratory infections was significantly lower in the group receiving prophylaxis than in the control group.

B. EFFECTIVENESS OF CHEMOPROPHYLAXIS IN THREE BACTERIAL INFECTIONS

It has been pointed out that the effectiveness of chemoprophylaxis in the respiratory tract is limited to bacterial infections. The effectiveness of sulfadiazine in preventing these bacterial diseases is, moreover, determined by the susceptibility of the causative agent to concentrations of 0.5 to 1.0 mgm. per cent of sulfadiazine on the mucous membranes of the respiratory tract. Meningococcus was found most susceptible; hemolytic streptococcus, in most instances, proved highly susceptible. There was great variation in the susceptibility of pneumococcus.

1. *Effect on Cerebrospinal Fever:* This disease was eliminated by chemoprophylaxis. Chart 6 illustrates the effect of the administration

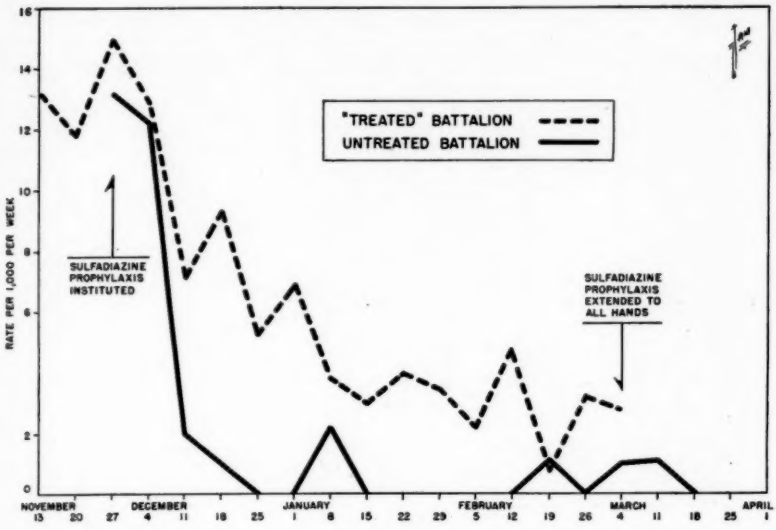

Chart 5. Morbidity rates for respiratory diseases during and following an outbreak of influenza in two battalions of 1,000 men each.

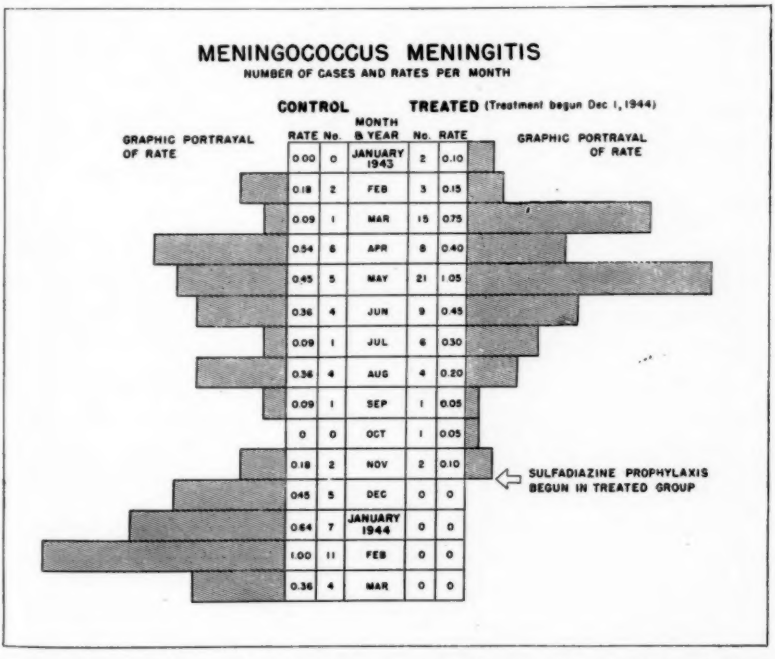
MENINGOCOCCUS MENINGITIS
NUMBER OF CASES AND RATES PER MONTH
CONTROL
TREATED (Treatment begun Dec 1, 1944)
GRAPHIC PORTRAYAL OF RATE
RATE No.
MONTH & YEAR
No. RATE
GRAPHIC PORTRAYAL OF RATE
0.00 0 JANUARY 1943 2 0.10
0.18 2 FEB 3 0.15
0.09 1 MAR 15 0.75
0.54 6 APR 8 0.40
0.45 5 MAY 21 1.05
0.36 4 JUN 9 0.45
0.09 1 JUL 6 0.30
0.36 4 AUG 4 0.20
0.09 1 SEP 1 0.05
0 0 OCT 1 0.05
0.18 2 NOV 2 0.10
SULFADIAZINE PROPHYLAXIS BEGUN IN TREATED GROUP
0.45 5 DEC 0 0
0.64 7 JANUARY 1944 0 0
1.00 11 FEB 0 0
0.36 4 MAR 0 0

Chart 6. The incidence of meningococcus meningitis on a large training station. Chemoprophylaxis was instituted on 1 December 1943 in 30,000 recruits.

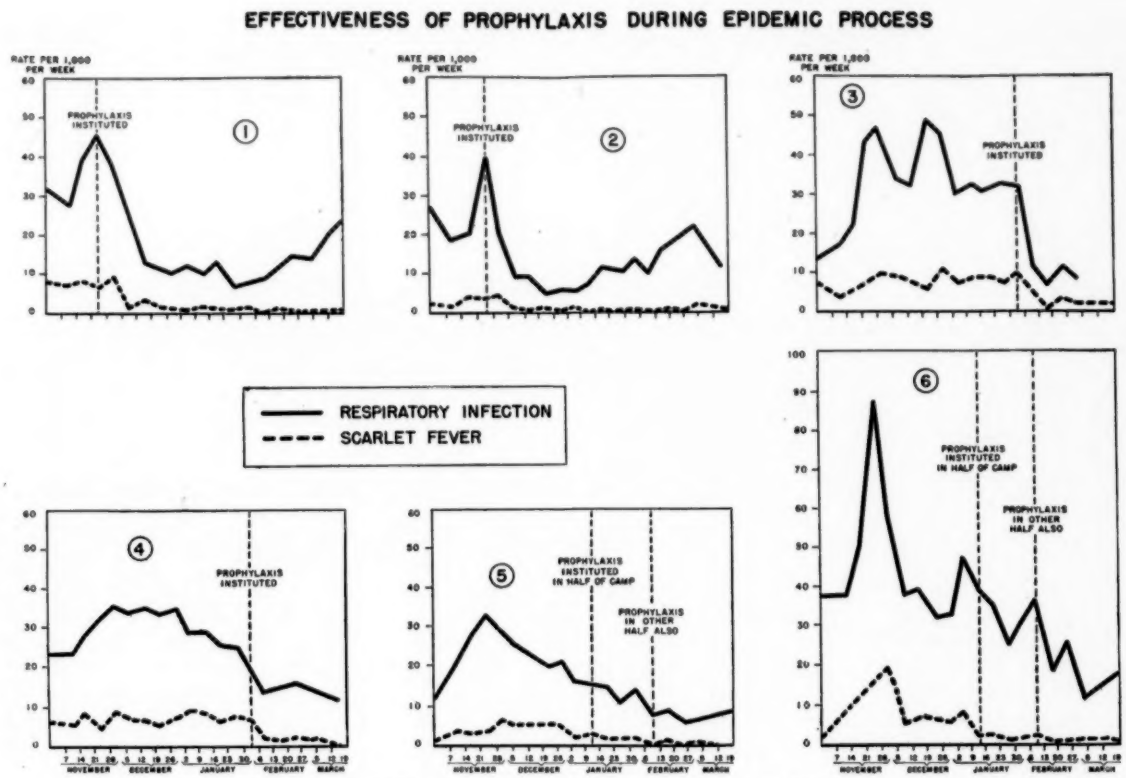

Chart 7. Morbidity rates for scarlet fever and respiratory infections before and following chemoprophylaxis in camps of 5,000 men.

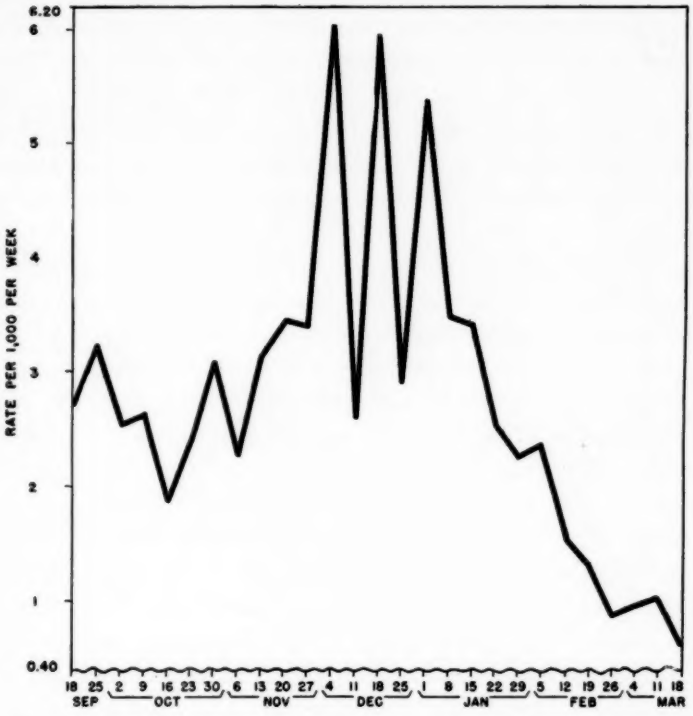

Chart 8. Morbidity rates for scarlet fever among 50,000 men. Chemoprophylaxis was instituted among 10,000 men in December 1943 and extended to 30,000 men in January 1944.

of sulfadiazine, 1.0 gram daily, in a camp where 30,000 recruits received prophylaxis and 30,000 recruits were observed as controls.

2. *Effect on Scarlet Fever:* Chemoprophylaxis was highly effective in preventing scarlet fever. At one training center, where 15,000 recruits received prophylaxis for three months and 25,000 for three subsequent months, scarlet fever was eliminated in groups receiving prophylaxis. This training center was situated in New York State and had previously experienced high morbidity rates for scarlet fever.

The institution of sulfadiazine prophylaxis at camps where scarlet fever was already epidemic was also found highly effective. Irrespective of whether the epidemic was in an early stage, at its height, or subsiding, chemoprophylaxis almost eliminated scarlet fever. The most

severe test given sulfadiazine during this program was at a Naval Training Center in northern Idaho. Both virus and bacterial respiratory pathogens were widely disseminated throughout this activity. The institution of chemoprophylaxis in each camp was followed by a prompt reduction in the incidence of scarlet fever. This is shown in Chart 7. The extension of sulfadiazine prophylaxis to the entire activity was followed by a reduction in the morbidity rate from 6 to 0.6 per 1,000 per week. This is shown in Chart 8.

3. *Effect on Pneumonia:* At some stations chemoprophylaxis lowered the incidence of pneumonia by 50 to 80 per cent. At other stations control measures were ineffective. This variation was associated chiefly with two factors: (a) the prevalence of atypical pneumonia and (b) the prevalence of drug-resistant strains of pneumococcus. At one activity in Oklahoma, most of the cases of pneumonia were atypical. At another activity in Idaho, the prevalent types of pneumococcus were found to be resistant to sulfadiazine concentrations of 2 mgm. per cent but susceptible to therapeutic blood levels of sulfadiazine (over 5 mgm. per cent). Sulfadiazine prophylaxis eliminated primary streptococcal pneumonia but failed to influence the pneumonia morbidity rate at this station while drug-resistant strains of pneumococcus were prevalent. This failure, shown in Chart 9, illustrates what may be expected if epidemic strains of hemolytic streptococcus or meningococcus are sulfonamide-resistant.

Observations on Dosage and Schedule of Sulfadiazine Administration

Two daily dosages, 1.0 gram and 0.5 gram, were tested in this study. Companies were assigned odd or even numbers alternately at the Receiving Unit; the odd-numbered companies received one dosage, the even-numbered companies the other. A random distribution of such environmental influences as barracking, time in camp, messing, and other factors was assured. Careful physical examinations of patients with respiratory illnesses were made by the medical officers conducting the investigation, and throat cultures were obtained to determine whether these diseases were caused by bacterial agents.

The findings indicated that there was slightly more streptococcal illness among the group receiving 0.5 gram of sulfadiazine daily than among the group receiving 1.0 gram daily. In some camps, no statisti-

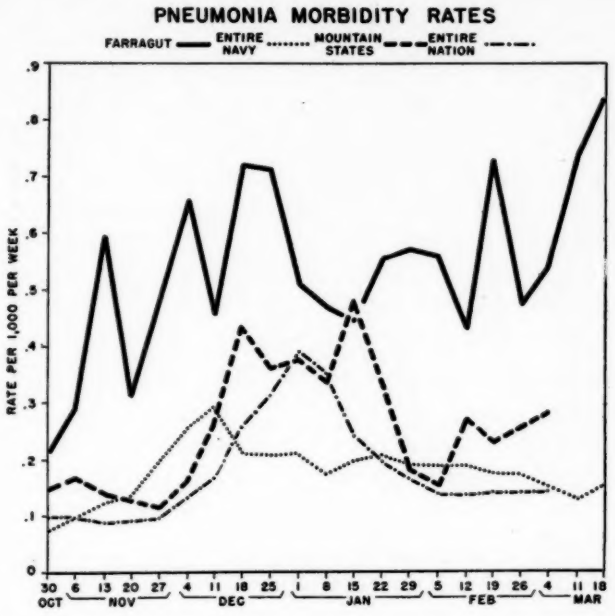

Chart 9. Morbidity rates for pneumonia. The entire station received chemoprophylaxis in March 1944.

cally significant difference in the effectiveness of the two drug dosages was demonstrable; other camps showed statistically significant differences. This variation may well have been due to the character of the prevalent strains of hemolytic streptococcus.

In addition to a continuous daily dosage, several schedules for administration were tested, such as, twice weekly, alternate weeks, alternate days. These schedules were found less effective and more difficult to administer than continuous daily prophylaxis.

Potential Untoward Effects of Chemoprophylaxis

More than 600,000 men received sulfadiazine and there were approximately 3,000,000 man-weeks in this control program. Untoward effects anticipated include: (1) a high incidence of drug reactions; (2) severe reactions terminating fatally; (3) sensitization of a large number of personnel; (4) initiation of sulfonamide-fastness among prevalent strains of hemolytic streptococcus. Each of the above points

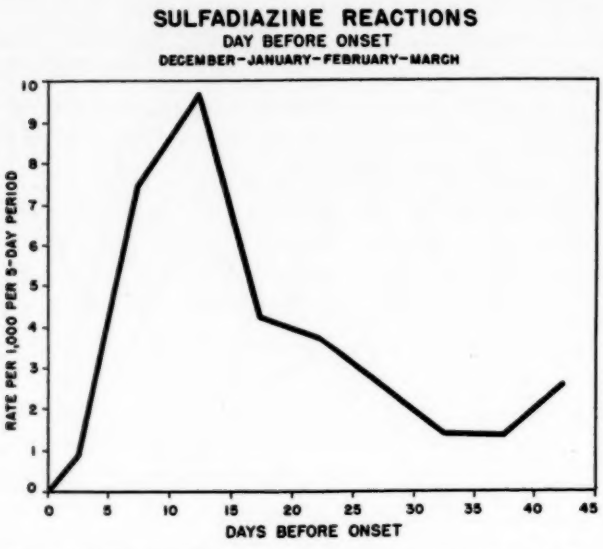

Chart 10. The distribution of sulfadiazine reactions in relation to duration of chemoprophylaxis.

was carefully investigated, and the findings were as follows:

1. The incidence of mild reactions was approximately 0.5 per cent. Nearly all of these reactions were dermal. Only half of the reactors were found sensitive to sulfadiazine on retesting with 1.0 gram of sulfadiazine. There were no renal complications from prophylaxis. Most of the reactions occurred during the first three weeks; there were a few immediate reactions among men who had previously received sulfonamide therapy; there were a few reactions as late as forty days after the institution of prophylaxis; the peak occurred between ten and fifteen days. This is shown in Chart 10.

2. Severe sulfonamide diseases occurred once in each 10,000 individuals, an incidence of 0.01 per cent. These were either exfoliative dermatitis or granulocytopenia. Altogether, thirty-nine men developed serious reactions. These reactions appeared to be reversible unless followed by sulfadiazine therapy. Fourteen deaths occurred among these 600,000 men from all causes, one from leukemia, two from granulocytopenia probably caused by prophylaxis, eleven from sulfonamide therapy administered to men with mild sulfadiazine reactions. There

were, also, two sulfonamide deaths in the control groups who received chemotherapy but no prophylaxis. After substituting the use of penicillin in place of sulfonamides for the treatment of these patients, there were no deaths among 350,000 men who received prophylaxis.

3. Sensitization did not appear to be produced by prophylaxis. The evidence for this is as follows:

a. The subjects who manifested reactivity to sulfonamide prophylaxis after the first day gave no history of previous sulfonamide therapy. This indicates that they had not been sensitized in the past.

b. Although about 5 per cent of human subjects develop reactions from sulfadiazine therapy, only 0.5 per cent developed reactions from sulfadiazine prophylaxis. This indicated that prophylaxis per se was not sensitizing.

c. Continuing prophylaxis in several groups for as long as from three to six months did not increase the percentage of reactions. This indicates that prolonged prophylaxis did not sensitize.

d. Stopping prophylaxis during alternate weeks or alternate months was followed by *no* increase in the incidence of reactions. Subjects who did not react to the first course of prophylaxis were not sensitive to subsequent courses. The administration of sulfadiazine therapy to men who had previously tolerated prophylaxis did not cause reactions. This is a further indication that prophylaxis had not sensitized.

4. Sulfonamide-fastness of prevalent strains of hemolytic streptococcus: Drug-fast strains of this bacterium were not detected clinically during this control program. It appeared that chemoprophylaxis does not favor the development of drug-fastness. The evidence for this is as follows:

a. There was no general increase in the prevalence of any serologic type of hemolytic streptococcus in the groups on prophylaxis during the first five months of this program.*

b. There was no increase in the proportion of hemolytic streptococci in the throat flora of individuals throughout the period of prophylaxis.

c. There was no increase in streptococcal morbidity throughout the period of prophylaxis.

Sulfadiazine prophylaxis was, however, only 85 per cent effective

* During the sixth month of this program, type 19 became predominant at several Naval activities. Subsequent in vitro tests showed that strains of type 19 at one Naval activity were sulfadiazine-resistant.

in preventing the implantation of hemolytic streptococcus. Some strains were able to infect individuals who had ingested 1.0 gram of sulfadiazine daily and who maintained a blood level of 2 mgm. per cent. The explanation for this phenomenon is not yet known. It has been suggested that these individuals may have inhaled a heavy inoculum, may have been infected by direct contact, may have had a low concentration of sulfadiazine in the secretions of the respiratory tract, may have insufflated, during swimming instruction, purulent matter containing living microorganisms and cellular debris which acted as a sulfonamide inhibitor and afforded protection to the respiratory pathogen. These possibilities are real. However, another possibility which may be of much greater significance is the resistance of the microörganism to prophylactic doses of sulfadiazine.

That sulfonamide-fast strains were not prevalent during this program is shown by the fact that those individuals who contracted streptococcal respiratory tract infections while receiving prophylaxis responded satisfactorily to therapeutic doses of sulfadiazine. That sulfonamide resistance did not develop generally is shown by the fact that there was no increase in streptococcal morbidity throughout six months of prophylaxis. However, the typing results of May 1944 suggest that type 19 may have developed resistance to small concentrations of sulfadiazine. During this final month of the program, type 19 became the predominant organism at several Naval activities. At one activity where all hands received prophylaxis, the predominant type disappeared and type 19 was the causative agent in practically all respiratory infections.

Final solution of the problem of bacterial resistance to sulfadiazine has awaited the development of an "inhibitor free" medium which will support normal growth of all strains of Group A hemolytic streptococcus. Such a medium has recently been developed in the Typing Laboratory at Bethesda and appropriate studies are now being made to determine whether strains recovered after six months of prophylaxis are more resistant to sulfadiazine than strains recovered and frozen at the onset of this program. A final opinion will be forthcoming with the results of these cultural studies. At present, the possibility that some strains of Group A hemolytic streptococcus are resistant to 1 mgm. per cent of sulfadiazine in the secretions of the respiratory tract seems real. This may well be the most important limiting factor of chemoprophylaxis in preventing implantation of Group A hemolytic streptococcus.

An Appraisal of Mass Chemoprophylaxis

This report represents the observations and consensus of opinion of eight Navy epidemiology units. The data included come from the labors of hundreds of officers, petty officers and corpsmen. The material is obtained from large Naval training activities in all Naval districts of the United States where streptococcal infections are prevalent. The design of the prophylactic program was blueprinted to meet the needs of these stations with their individual respiratory disease problems. The execution of each program varied with the size, ability, imagination, and resourcefulness of the epidemiology unit. The serologic typing of hemolytic streptococcus was done under constant conditions in one laboratory. With this exception, each program encountered variables patently beyond control. Nevertheless, given one blueprint based on the fact that the presence of sulfadiazine molecules on the mucous membranes exerts a bacteriostatic effect on respiratory pathogens, given one-half million men to protect altogether, given one sulfonamide to administer, and given one objective, all these epidemiology units reported one conclusion: The strategy of mass chemoprophylaxis is fundamentally sound.

The degree of effectiveness of sulfadiazine prophylaxis is shown in these studies to be determined in part by the characteristics of the bacteria which the drug encountered. For example, the pathogenesis of a meningococcal infection seems to depend upon the spreading of this organism throughout a "herd;" the pathogenesis of a streptococcal infection seems to depend upon implantation of a virulent strain in the susceptible host; the pathogenesis of pneumococcal pneumonia seems to depend upon the lowering of resistance of a carrier. The effectiveness of chemoprophylaxis in these diseases varies accordingly.

1. For example, it is known that so long as the carrier rate of meningococcus is kept low, cerebrospinal fever rarely develops. The presence of small amounts of sulfadiazine exerts such a highly bacteriostatic effect on meningococcus that the carrier rate is reduced to a minimum. Chemoprophylaxis has, therefore, proved to be a perfect protection against cerebrospinal fever in these one-half million men.

2. Previous studies have shown that sulfadiazine, either in prophylactic or therapeutic dosage, has little effect on the throat flora of carriers of hemolytic streptococcus. The present observations have proved

confirmatory. In addition, however, they have shown that the presence of small concentrations of sulfadiazine in the nasopharyngeal secretions will "screen out" hemolytic streptococcus. Implantation of this bacterium was prevented in most instances, irrespective of the pathogenicity of the prevalent strains. Only in a small percentage of instances did this microörganism penetrate the bacteriostatic effect of sulfadiazine. This occurred after the individual had been ingesting one gram of drug daily for a period of weeks and was maintaining a satisfactory blood level; this was observed in areas where the exposure to streptococcal infections was greatest and especially among recruits receiving swimming lessons; this was most striking at the time that the incidence of measles was high. Nevertheless, even under these conditions the presence of sulfadiazine in the nasopharyngeal secretions usually prevented the implantation of a new strain of hemolytic streptococcus. By this achievement chemoprophylaxis was at least 85 per cent effective in preventing streptococcal infections.

3. Previous studies have also shown that mechanisms essential for the pathogenesis of pneumonia are different from those of meningococcal and streptococcal infections. An individual may be a carrier of pneumococcus for many weeks and escape disease until an episode upsets the host-parasite balance in favor of the microörganism. The present observations show that a considerable percentage of the individuals developed pneumococcal lung infections and pneumococcal otitis media while maintaining a sulfadiazine blood level of about 2 mgm. per cent. One factor in the pathogenesis of these diseases may have been indoor swimming. Another factor, demonstrated in certain instances, was the prevalence of a sulfonamide-resistant strain of pneumococci.

Summary

Sulfadiazine prophylaxis has been administered to approximately 600,000 Naval personnel and approximately 300,000 similar personnel have been observed as controls.

The institution of this measure was followed by a marked reduction in the morbidity rates for respiratory diseases.

The incidence of respiratory symptoms observed at sick call was significantly lowered.

Hospital admissions for respiratory diseases were reduced from rates varying between 5 and 18 per 1,000 per month to less than 1 per 1,000 per month.

Meningococcal infections were eliminated.

The incidence of pneumococcal pneumonia was significantly lowered at most Naval stations.

Morbidity rates for respiratory diseases caused by filtrable viruses were unaffected.

The most effective dosage tested was 1.0 gram daily.

The administration of 0.5 gram of sulfadiazine daily was also found effective and was followed by fewer untoward reactions.

Mild, untoward drug reactions were observed in about 0.5 per cent. Severe reactions ocurred in 0.01 per cent of men taking 1.0 gram of sulfadiazine daily.

Sensitization of Naval personnel to sulfonamides and the development of sulfadiazine-fast respiratory pathogens did not occur.

This paper has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

The author is indebted for the data set forth in this paper to the following Epidemiology Units of the U. S. Navy:

Epidemiology Unit #12
Epidemiology Unit #13
Epidemiology Unit #19
Epidemiology Unit #22
Epidemiology Unit #42
Epidemiology Unit #43
Epidemiology Unit #67
Epidemiology Unit #89

DISTANT SECONDARY CIRCULATORY AND VASOMOTOR REACTIONS TO ACCIDENTAL ELECTRIC SHOCK*

GEORGE H. HYSLOP

WHEN the electrical current traverses the body, its pathway is the shortest distance between entry and exit. What happens to tissues depends upon the amount of amperage and duration of the current.

Tissue reactions may be physiological or pathological. When the electric energy of the current is turned into heat, tissues may be burned and destroyed.

L. Alexander[1] states that 25 milliamperes or more may produce permanent damage to nerve tissues and blood vessels. A critical level for morphological alteration of nerve tissue is 30 milliamperes per 3 mm. of nerve diameter for shocks of 5 seconds duration.[2]

One may define direct primary effects as limited to tissues traversed by the current. Indirect or secondary effects are those which occur in other tissues due to reaction originating in tissues traversed and directly affected by the current.

Prior to a few years ago, certain writers concluded that the blood vessels have less resistance to current than other tissues, or are especially vulnerable, thus allowing part of the current to traverse the body in a branching manner, and cause lesions in tissues supplied by these vessels.

This theory was probably devised to explain certain clinical phenomena, such as an immediate or delayed cerebral reaction to a current which passed perhaps from arm to arm, or from an arm to a leg, and traversed the trunk.

A. W. Weeks and L. Alexander[3] demonstrated that the current chooses the shortest path from contact to contact without deflection by anatomical landmarks (thus indicating that the body acts as "a structureless gel"). They also demonstrated that in tissues adjacent to, but away from the current main path, the effective current conducted

* Read January 9 at the joint meeting of The Section of Neurology and Psychiatry and The New York Neurological Society.

rapidly decreases, that is, there is practically no diffusion of the current away or distant from its main path. Also, they demonstrated that when the current passes from a hind foot to a fore foot, the amounts traversing the aorta, vena cava, spinal cord and long back muscles were similar. As for blood vessels, it has been shown by F. Echlin[4] that when the current traverses arteries, there is an initial constriction followed by a period of dilatation which may be severe and prolonged and cause secondary hemolysis of the blood in the veins. These reactions are limited to vessels traversed by the current.

However, in certain fatal cases, there may be widespread filling of blood vessels with non-clotted blood, called "hemogenized blood", which is regarded as a secondary effect of prolonged respiratory paralysis. Such respiratory paralysis may occur in individuals in whom the current has not traversed the respiratory center, but where there has been prolonged tetanic spasm of the muscles of the body, so that respiratory movements have been interrupted.

A number of authors have commented on the blood pressure responses to electric shock. I have not found in the literature any statistical evaluation of clinical material bearing on this point. It seems reasonable, however, to hold that if there is a systemic reaction to injury by the electrical current, then the blood pressure response would be similar to what occurs in systemic shock due to other causes. If the current directly affects the respiratory or circulatory centers in the medulla, or if it produces a definite effect upon either the heart muscle or the innervation of the heart, blood pressure reaction is to be expected with a drop where function is depressed. As for the heart, its rhythm is disturbed by non-dangerous amounts of current, and the pulse will become rapid and somewhat irregular. Ventricular fibrillation, which is fatal in practically every instance (in experimental animals immediate counter shock may abolish the fibrillation) occurs when the current reaches an amount of something less than 100 milliamperes continued for a second or longer.

L. Alexander[5] states as follows: "In hand to hand contacts cerebral changes are not due directly to the current but are caused by the prolonged circulatory disturbances produced by passage of the current through the heart and the endings of the vagus nerve."

Instances are known in which no loss of consciousness occurred, and the current pathway did not reach the brain, but within from a

few minutes to two or three days, the victim manifested signs of some focal reaction in the brain. As yet no satisfactory explanation has been offered for such delayed and distant tissue reactions.

If severe convulsions or prolonged coma are immediate effects of electrical shock, local cerebral circulatory reaction is not surprising. If there were a definite disturbance of heart function, or if a marked and prolonged change in blood pressure occurred, one might hypothecate some focal cerebral circulatory disturbance.

The literature cites instances of basal ganglia and other focal cerebral lesions as precipitated or due to electrical shock-effects in cases where the electrical current did not pass through or directly affect the brain. I will exclude from consideration the cases published without adequate evidence as to the physics involved or proper attention to the clinical facts. In a number of reported cases, the cerebral lesions are not progressive, and the clinical picture is not that of similar lesions due to other causes.

The trunk contains the great sympathetic ganglia and plexuses. If these tissues are directly affected by current traversing the trunk, it is physiologically entirely possible that stimuli from the splanchnic, celiac, and other abdominal sympathetic ganglia would have such an effect upon the great blood vessels in the trunk, that the circulation to distant parts of the body would be at least temporarily altered without any structural change whatever in these distant blood vessels.

It is known that stimulation of the cervical sympathetic ganglia affects cerebral circulation. Impulses originating in the trunk sympathetic ganglia undoubtedly may spread to the cervical sympathetic chain.

I have not found in the literature any discussion or experiments bearing upon this hypothetical physiological reaction.

However, such a reaction offers a theoretical basis to account for such distant reactions as those mentioned as producing even delayed focal cerebral lesions.

I. M. Scheinker[6] in a paper entitled, "Vasoparalysis of the Central Nervous System, A Characteristic Vascular Syndrome," presents certain conclusions which are perhaps germane.

I quote as follows: "Paralytic dilation of a blood vessel directly stimulated is accompanied by a slowing down of the blood stream which, if sufficient in degree, may result in stasis."

He quotes T. J. Putnam as observing that stimulation of cervical

sympathetic fibers causes an average reduction in blood flow of approximately 15 per cent, the systemic artery blood pressure remaining constant.

He quotes Nedzel as observing that after injections of pitressin, "a typical picture of white stasis was observed" to occur in the adjacent region with associated degenerative lesions of perivascular nerve tissue.

Scheinker commented also on the passive hyperemia observed in agonal states, and the instances in which great dilation of blood vessels is associated with structural changes of the vessel wall, resulting in increased permeability for serous fluid and red blood cells.

Scheinker's paper is concerned chiefly with the effect of mechanical trauma on blood vessels. However, he points out that profound circulatory disturbances may be seen in regions remote from the direct influence of the irritant stimulus, thus indicating that the stimulus is probably transmitted over a neurovascular network to the distant subdivision of the vascular tree. If there is circulatory stasis, there is local accumulation of carbon dioxide which is a particularly active vasodilator. If it continues to accumulate, there is further vascular dilation and increased permeability of the vessel wall with actual degeneration and necrosis of the vessel walls if the alterations are sufficiently severe.

Thus, the essential vascular factor for involvement of surrounding tissues is the increased permeability of the vessel wall.

It has been amply demonstrated that the effect of electrical current on the blood vessels directly traversed is such that degenerative changes in surrounding tissue may be slow in development. It is an adage that electrical superficial burns may seem inconsequential at first, but that, due to delayed effects, there may be later extensive necrosis of the tissues injured.

If current traverses the cervical sympathetic, it is not unlikely that the brain vessels may be affected. If when the splanchnic and abdominal sympathetic ganglia are violently stimulated and there may be spread of the impulses to the cervical sympathetic, brain vessel reaction could occur. There might be immediate transient symptoms of focal nature if the brain vessel effects were limited to brief spasm. If the vessel wall were to suffer structural damage with impairment of permeability, effects on surrounding brain tissue might be delayed so that focal clinical symptoms would not be evident for even a few days.

(See p. 306 for References)

REFERENCES

1. Alexander, L. Electrical injuries to the central nervous system, *M. Clin. North America*, 1938, *22*:663.
2. Alexander, L. and Weeks, A. W. Electric shock; importance of path, distribution and density of current in determining symptoms and pathology, *Am. J. Path.*, 1941, *17*:601.
3. Weeks, A. W. and Alexander, L. The distribution of electric current in the animal body; an experimental investigation of 60-cycle alternating current, *J. Indust. Hyg. & Toxicol.*, 1939, *21*:517.
4. Echlin, F. A. Vasospasm and focal cerebral ischemia, *Arch. Neurol. & Psychiat.*, 1942, *47*:77.
5. Alexander, L. Electrical injuries of the nervous system, *Arch. Neurol. & Psychiat.*, 1942, *47*:179.
6. Scheinker, I. M. Vasoparalysis of the central nervous system, a characteristic vascular syndrome, *Arch. Neurol & Psychiat.*, 1944, *52*:43.

THE ROLE OF BILATERAL ORCHIECTOMY IN THE TREATMENT OF CARCINOMA OF THE PROSTATE GLAND*

A report of 82 cases

W. W. Scott and J. A. Benjamin

From the Department of Surgery, Division of Urology, of the University of Rochester, School of Medicine and Dentistry

Introduction

On no branch of cancer research, since 1941, has the spotlight of medical interest been so definitely focused as that of carcinoma of the prostate gland. This interest was aroused by a series of brilliant experimental and clinical studies that fortunately appeared in a logical and orderly sequence. The series which was initiated by Kutscher and Wolbergs in 1935[1] with the discovery of large amounts of the phosphatase enzyme in the adult monkey and human prostate gland, culminated in the splendid experimental and clinical studies by Huggins and his associates[2,3] on the effects of bilateral orchiectomy upon patients with carcinoma of the prostate gland. At last it seemed as though some of the mysterious factors controlling the development and especially the growth of carcinoma of the prostate gland had been discovered and a type of therapy based upon sound experimental and clinical observations and offering a very considerable degree of relief had been introduced. As a result, bilateral orchiectomy in the treatment of carcinoma of the prostate gland was accepted with enthusiasm by the medical profession.

Even before the report of Huggins and his associates others had observed the effects of surgical castration and irradiation sterilization upon patients with carcinoma of the prostate gland. Young[4] had re-

* This investigation was supported with funds from the Dr. Henry C. Buswell Memorial.
Read before the joint meeting of the Section of Genito-Urinary Surgery of The New York Academy of Medicine and the New York Society of The American Urological Association, Yale Club, New York City, December 14, 1944.

ported failures in two cases of carcinoma of the prostate gland following bilateral orchiectomy and Counseller[5] had observed a regression of metastases due to carcinoma of the prostate following sterilization by irradiation. Randall[6] in 1942 reported a study of five patients who were castrated for carcinoma of the prostate, seven, eight, and nine years previously. Of these, one was living six and one-half years but had definite evidence of metastases. Munger in 1941[7] reported eight patients treated by testicular irradiation, two of whom had had metastases of the pelvic bones six and three years respectively.

In the time that has elapsed since the report of Huggins and his associates on this type of therapy, many investigators have had an opportunity to observe its effects, conduct supplementary experimental and clinical studies, and report their findings. Excellent reports by Chute, Willetts and Gens;[8] Nesbit and Cummings;[9] Alyea and Henderson;[10] Emmett and Hamm;[11] Dean, Woodard and Twombly,[12] and many others, confirmed for the most part the findings of Huggins and his associates. The question of hormonal inter-relationship between the testes and the prostate and pituitary gland was introduced in at least two of the above reports. Likewise the role of the 17-ketosteroids as an index of male hormonal activity was considered but no definite conclusions were drawn. Dean et al.[12] suggested that fractionation of these might give valuable information concerning their biologic activity. The results obtained by Kretschmer[13] in reporting eleven cases were apparently less satisfactory than those obtained by many of the other writers. In his series three patients were dead, five were not helped, two were improved, and one was reported as feeling well.

We were moved to review the results obtained by this method in our series of eighty-two patients not only because there seemed to be differences of opinion as to its effectiveness but for another, and to us a much more important reason. We were under the impression that some of our patients after orchiectomy had enjoyed a varying period of marked improvement that was followed by a relapse characterized by a rapid return to their condition before treatment or even worse. It was our hope that by studying the course of the patients treated by this method we might, in selected cases, be able to recognize and grasp a fleeting opportunity during the period of marked improvement, to obtain a much more satisfactory result by means of radical perineal prostatectomy.

Results

The statistics which follow were derived from a study of the results obtained by bilateral orchiectomy upon 82 consecutive patients in various stages of development of carcinoma of the prostate gland in the period between January 1941 and June 1944.

Age: The 82 patients were studied for each decade of life and no relation was found between the age of patient and his response to treatment. The average age for all the patients was 69.4 years with a range of 55-84 years.

Pathology: The clinical diagnosis of carcinoma of the prostate was confirmed by microscopic study of stained sections in 59 of the 82 cases. Of these the tissue was obtained by means of a punch biopsy prior to orchiectomy in 29 cases. In the remaining cases the tissue was obtained at the time of transurethral resection for the relief of urinary obstruction. In 83.5 per cent of the cases the growth was predominantly adenocarcinoma while in 16.5 per cent it was predominantly a type of undifferentiated carcinoma. Sixty per cent of the patients in the latter group and 26.7 per cent in the former were known to be dead at the completion of this study.

Acid and alkaline phosphatase studies: Thirty-seven of the seventy-six patients upon whom serum acid phosphatase studies were made had normal preoperative readings. Of these the immediate (first two months) and remote readings remained normal except for one temporary slight increase in each category. There was no follow-up on two patients.

The acid phosphatase readings were high before operation on thirty-nine patients. The results in these cases were: immediate drop (within two months) to normal, where it remained, fourteen; immediate drop to normal but remote increase to above normal, four; no immediate change but remote return to normal, three; immediate return to normal but no remote follow-up, four; no immediate readings but remote studies normal, two; very temporary increase followed by immediate return to normal, where it remained, two; immediate increase but no follow-up, one; and no immediate and remote studies in nine cases.

Of the thirty-seven patients with normal acid phosphatase readings before operation eight were dead but at least three of these did not die from carcinoma of the prostate. Seventeen of the thirty-nine patients

who had high acid phosphatase readings before operation were dead. The survival rate was better than twice as great in the group with normal readings before operation.

At first we did not make a routine serum alkaline phosphatase study on our patients with carcinoma of the prostate because we believed that while it did indicate the response to bone injury it could give us little if any more information of prognostic value than we were able to obtain from our x-ray and serum acid phosphatase studies in our cases of carcinoma of the prostate. Later because we feared that we might be neglecting a source of considerable prognostic information, we decided to make serum alkaline phosphatase determinations.

Twenty patients had alkaline phosphatase studies made before operation. From the fifteen patients with normal readings before operation the following observations were made: Six maintained normal immediate and remote readings; four experienced an immediate increase but returned slowly to normal; three maintained an immediate normal reading but experienced a gradual increase, and two had normal immediate studies but no follow-up readings were recorded.

Five patients had elevated alkaline phosphatase readings before operation and the following observations were made: Immediate and remote readings remained about the same as preoperative in one; immediate increase followed by a drop and then a gradual steady increase in one; very temporary increase followed by a return to normal where it remained, one case, and two patients with an immediate increase had no follow-up studies.

Two of the five patients with elevated alkaline phosphatase readings before operation have already died of the disease. Three of the fifteen patients with normal preoperative alkaline serum phosphatase were dead when this study was completed.

We have elected to use as the normal for serum acid and alkaline phosphatase readings 0-5 and 0-10 King-Armstrong units respectively.

X-ray survey: The x-ray survey consisted of a routine check of the pelvic bones, lower end of the vertebral column, and upper ends of the femurs. More extensive studies were made when indicated. The results are shown in Table 1.

Comment: Fourteen of the twenty-six patients with positive x-ray studies for metastases were known to be dead at the time this study was completed. Eleven of the fifty-two patients with negative preoper-

TABLE I

RESULT OF X-RAY SURVEY FOR METASTASES IN 82 CASES

Positive before, no change	2
Positive before, progressed	13
Positive before, regressed	3
Positive before, no follow-up	8
Negative before, became positive	5
Negative before, remained negative	19
Negative before, no follow-up	28
No x-ray survey before operation	4
	82

TABLE II

TIME INTERVAL BETWEEN ORCHIECTOMY AND RESECTION

Time in months	1—2	6—12	18—24	24—30	*Total number of patients*
Number of patients	25	2	2	1	30

ative x-ray studies were known to be dead but at least three of them did not die from carcinoma of the prostate gland.

Changes in the prostatic region: The result of this therapy upon the prostate gland in eighty-two cases was as follows: Unchanged 26 per cent, regression occurred in 54 per cent, growth progressed in 2 per cent, and no follow-up report on 17 per cent. When the regression percentage was determined on the basis of the number of patients who had adequate follow-up rectal examinations, sixty-eight cases, it was found to be 66.2 per cent.

Operations for obstruction: It was necessary after bilateral orchiectomy to perform a transurethral resection for relief of urinary obstruction upon thirty patients.

It is of interest to note that twenty-five patients required resection within two months after orchiectomy. It is possible that some of these resections could have been avoided if the patients had not been confined to their bed after orchiectomy, and the dosage of stilbestrol had

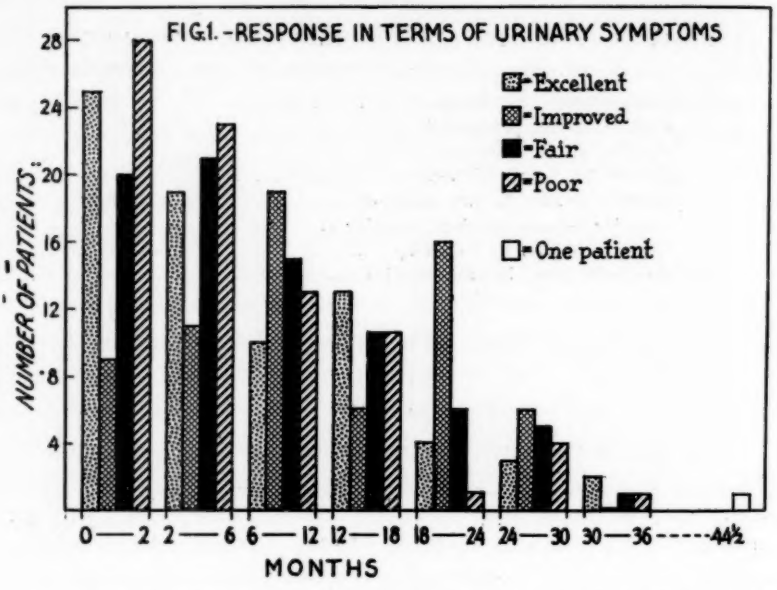

Fig. 1. Shows the time intervals in relation to the response of the patients in terms of urinary symptoms. Explanation of terminology is as follows: excellent, patient is free from urinary symptoms; improved, symptoms present but minimal; fair, symptoms disturbing but not progressive; poor, symptoms are very disturbing and no response to therapy.

been materially increased. Of further interest is the finding in our data that within two months 35.2 per cent of the patients in the group without metastases had to have resections, whereas only 24.4 per cent of the group with metastases had to have resection.

Another interesting feature came to our attention during the study of the operative data. In the non-metastatic group, which included thirty-seven cases, nine patients had had a conservative perineal prostatectomy for urinary obstruction before orchiectomy, and at the completion of this study all were alive. In the metastatic group, which included forty-five patients, two of these had had suprapubic prostatectomy for obstruction before orchiectomy and both were dead.

General response to therapy: In an effort to learn as much as we could about the effectiveness of this therapy upon the urinary and metastatic symptoms of the patients, their degree of response was estimated in terms of their condition at stated time intervals after

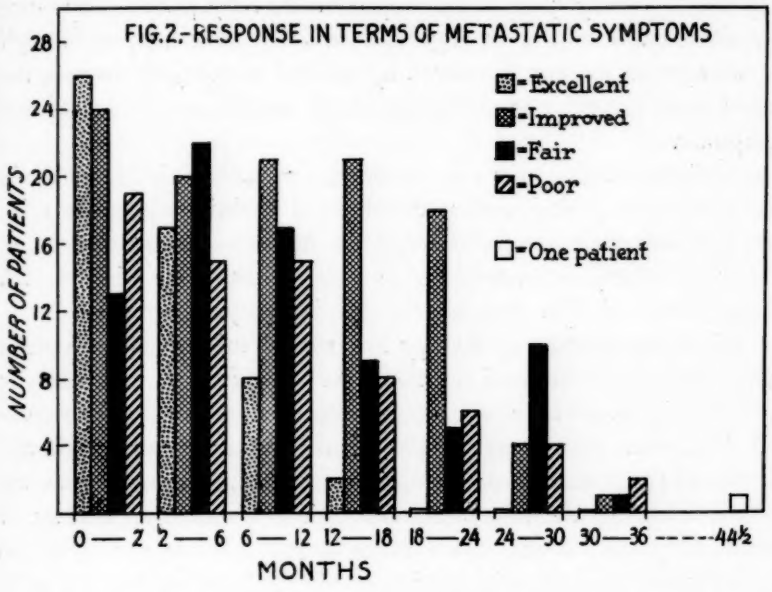

Fig. 2. Shows the time intervals in relation to the response of the patients in terms of metastatic symptoms. Explanation of terminology is as follows, excellent, patient has no complaints; improved, definite improvement but not completely free of complaints; fair, improvement is slight but the disease is temporarily checked; poor, no response to therapy, and patient is incapacitated.

orchiectomy. On this basis the patients have been divided into groups according to their type of response which has been conveniently classified as excellent, improved, fair and poor (Figs. 1 and 2).

Response in terms of urinary symptoms: A study of Fig. 1 showed that the early response of the patients as estimated in terms of urinary symptoms was relatively slow; in fact twenty-five patients required resection for relief of obstruction in the first two months after orchiectomy. During the first six months period the number of patients in the improved grouping was relatively less than in the following six to twenty-four months, showing a delayed response to therapy in some cases. However, at the end of thirty-six months there were but few patients alive and these were in poor condition.

Response in terms of metastatic symptoms: A study of Fig. 2 showed that the early response of the patients in terms of metastatic symptoms was much more pronounced after orchiectomy than in the case of

response to urinary symptoms during the same early period. The number of patients in the improved group continued rather constant through to twenty-four months. However, by the end of thirty-six months the results were quite similar to those obtained with respect to the urinary symptoms.

It is interesting to note that the number of patients in all groups in the 6-12 month period, both with reference to their response to urinary and metastatic symptoms, were about the same. However, at the end of thirty-six months only a few patients were alive in each classification and their progress was unsatisfactory.

When the response to therapy in terms of urinary and metastatic symptoms was considered in the light of the data presented by Bumpus[14] in his study of a group of untreated patients, some interesting differences were apparent. He found that 485 patients with carcinoma of the prostate gland, who had received no treatment from the time of onset of the first symptoms until death lived an average of about thirty-one months. The average length of life in our series was 35.4 months, a slight but definite increase in the length of life as a result of therapy. He also found that 66.7 per cent of the patients having metastases at the time of examination were dead in nine months, while our study showed that 40 per cent were dead in an average of 15.1 months. In other patients without metastases at the time of examination Bumpus noted that their length of life was twelve months. Our patients without metastases lived an average of 17.1 months; in fact one of these lived 44.5 months. At the time this study was completed 31.7 per cent of all the patients were dead. Therefore, we have some statistical evidence in the above data that orchiectomy offered definite benefits when determined in terms of length of life.

Discussion

From this study and a review of the literature there seems to be little doubt but that in the treatment of advanced carcinoma of the prostate, especially patients with symptoms of metastases, bilateral orchiectomy is a definite improvement over the therapeutic measures that were in use before its introduction. In the majority of these cases the immediate relief of pain, gain in appetite, increase in weight and the occasional decrease in urinary symptoms are often striking and most satisfactory. This clinical improvement is usually accompanied by

an immediate drop in acid serum phosphatase to or towards normal. If the alkaline serum phosphatase is elevated it may tend to increase for a short time and then drop toward or to normal. Of course there are unexplained exceptions to the above phosphatase reactions. In a small percentage of these cases there may be a temporary stop of the bony metastatic process or even regression. In a second and smaller group of patients the response to therapy is neither so marked nor so rapid but nevertheless it is definite and steady for a varying period of time. A third group, in which the response to therapy is at best only fair, is composed of patients who show but slight improvement or in whom the progress of the disease is apparently stopped for a time. In the last or fourth group are those patients who are not helped by this therapy. As the interval after treatment increases the number of patients in the excellent and improved groups steadily decreases so that when the period of between 24-30 months is reached the distribution of patients in each of the four response groups is about the same and very few are alive in any group. Therefore, while some patients are not helped by this therapy the majority obtain a varying degree of relief for a time and the average length of life after onset of symptoms and beginning of treatment is somewhat increased.

No study of the effects of bilateral orchiectomy is quite complete without a brief consideration of some of the untoward reactions that occasionally occur. The loss of sexual power while lamentable in the occasional case is usually a matter of secondary importance when viewed in the light of the patient's age and the marked improvement that sometimes results from this therapy. The unexplained swelling of the lower extremities that occasionally follows orchiectomy is usually quite temporary, disappearing in four or five months. The climacteric manifestations consisting of sweating, hot flashes, irritability, fatigue, etc., which occur in varying degree fortunately respond to estrogenic therapy. A postcastration gain of weight to an embarrassing degree is rare and was not seen in our series.

A great many of the reports on the effects of bilateral orchiectomy in carcinoma of the prostate have included observations on the beneficial results obtained from estrogenic therapy. Many believe that the response to this therapy, especially where large doses are well tolerated is quite comparable to that obtained by castration. In fact, Kahle and his associates[15] in a most encouraging report observed among other

beneficial effects, the regression of metastatic lymph nodes in 2 cases. From our review of the literature and our own experience with these two types of therapy we are not as yet certain as to their relative merits. We do believe that in a certain group of patients in whom the response to one of these therapeutic measures is slower than average, the supplementary use of the other sometimes causes an immediate satisfactory reaction. Except in those instances where one or the other of these therapeutic measures is contraindicated, the decision as to which type should be used and when it should be instituted must await further clinical observations. Inasmuch as the majority of the patients in our series requiring an operation for the relief of urinary obstruction were operated upon during the first two months after their orchiectomy we are now using large supplementary doses of stilbestrol, when tolerated, especially upon those patients who evidently have considerable obstruction.

While the decision as to whether or not a patient is a suitable candidate for a follow-up radical perineal prostatectomy is frequently influenced by findings that are peculiar to each patient, there are certain fundamental requirements that should be met by all of them. In so far as one can determine from the patient's symptoms, x-ray survey and phosphatase studies there should be no evidence of metastases. The local lesion as a result of bilateral orchiectomy or stilbestrol therapy or a combination of both must be sufficiently reduced in size so as to present a reasonable chance for its complete removal. Finally the patient's physical condition should at least be fair and his life expectancy should be more than three years. The idea of attempting the radical removal of the primary lesion after orchiectomy has evidently occurred to others. Vallett in 1944[16] reported a radical prostatectomy after orchiectomy for carcinoma of the prostate and a little later Parlow[17] advocated the same procedure in selected cases.

In the 12 months that followed our decision to perform the radical prostatectomy upon patients who met the requirements previously stated, 5 were found upon whom the procedure seemed to offer a fair chance of success. Two of these had been treated by orchiectomy alone, 2 by large doses of stilbestrol and one by a combination of both types of therapy. Unfortunately up to the present time only 2 of them have been operated upon. One patient who was prepared for operation by a combination of both types of therapy was operated

upon by Dr. A. L. Parlow, a member of our staff, and the other was prepared by stilbestrol therapy and operated upon by one of us. At the time of operation in both cases it seemed as though all of the local lesion had been removed. However, a study of microscopic serial sections made from both gross specimens suggested a strong possibility of at least a minimal extension beyond the field of operation. Therefore while the immediate result in both cases appears quite satisfactory the remote prospects are rather uncertain. It is our hope that at the very least the operation will prevent the occurrence of urinary obstruction and that it may greatly delay the development of a generalized process. One patient, prepared on stilbestrol therapy, felt so well that he married and because of objections on the part of his wife, who is much younger, has refused surgery. Of the two remaining patients who were prepared by bilateral orchiectomy one refused to have "any more cutting" and the other had a mild cerebral accident which seemed to make further surgery inadvisable. Because it necessitates but one operation and avoids the climacteric nervous disturbances which frequently follow bilateral orchiectomy, we believe that these patients should be prepared for radical surgery, where possible, by stilbestrol therapy. Furthermore in the event that it is impossible to remove the entire local lesion, bilateral orchiectomy could still be held in reserve for future use.

Conclusions

1. A study of the results obtained by bilateral orchiectomy in the treatment of 82 patients in various stages of carcinoma of the prostate gland has been presented.

2. In the majority of patients the early response of metastatic symptoms was much more rapid and satisfactory than had been obtained by the methods in common use before its introduction.

3. The early response of urinary symptoms was neither so frequent nor satisfactory.

4. A small percentage of patients received little or no benefit from this therapy.

5. Most of the patients treated by this method were either dead or had lost its initial benefits within thirty-six months.

6. In view of the discouraging end results following this therapy we believe that a follow-up radical perineal prostatectomy should be

very seriously considered, in selected cases, where the response to therapy is such that there is a reasonable chance for the removal of all or almost all of the primary lesion.

7. As yet there is no substitute for radical perineal prostatectomy for cancer of the prostate gland where the patient's condition and size and location of the lesion at the time of the first examination permits its complete removal.

REFERENCES

1. Kutscher, W. and Wolbergs, H. Prostataphosphatase, *Ztschr. f. physiol. Chem.*, 1935, *236*:237.
2. Huggins, C., Stevens, R. E., Jr. and Hodges, C. V. Studies on prostatic cancer; effects of castration on advanced carcinoma of prostate gland, *Arch. Surg.*, 1941, *43*:209.
3. Huggins, C. and Hodges, C. V. Studies on prostatic cancer; the effect of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate, *Cancer Research*, 1941, *1*:293.
4. Young, H. H. Cancer of the prostate, in *Modern Urology*, ed. by H. Cabot, Philadelphia, Lea and Febiger, 1936, v. *I*, p. 828.
5. Counseller, V. S. Discussion on Herrell, W. E. Relative incidence of oophorectomy in women with and without carcinoma of the breast, *Proc. Staff Meet., Mayo Clinic.*, 1936, *11*:788.
6. Randall, A. Eight-year results of castration for cancer of the prostate, *J. Urol.*, 1942, *48*:706.
7. Munger, A. D. Experiences in the treatment of carcinoma of the prostate with irradiation of the testicles, *J. Urol.*, 1941, *46*:1007.
8. Chute, R., Willetts, A. T. and Gens, J. P. Experiences in the treatment of carcinoma of the prostate with stilbestrol and with castration by the technique of intracapsular orchidectomy, *J. Urol.*, 1942, *48*:682.
9. Nesbit, R. M. and Cummings, R. H. Prostatic carcinoma treated by orchiectomy; a secondary report based on 75 cases observed for at least 21 months following operation, *J.A.M.A.*, 1944, *124*:80.
10. Alyea, E. P. and Henderson, A. F. Carcinoma of the prostate; immediate response to bilateral orchiectomy; clinical and x-ray evidence, *J.A.M.A.*, 1942, *120*:1099.
11. Emmett, J. L. and Hamm, R. S. Bilateral orchiectomy for carcinoma of the prostate gland; preliminary report, *S. Clin. North America*, 1944, *24*:943.
12. Dean, A. L., Woodard, H. Q. and Twombly, G. H. The endocrine treatment of cancers of the prostate, *J. Urol.*, 1943, *49*:108.
13. Kretschmer, H. L. Orchiectomy in the treatment of cancer of the prostate gland, *J.A.M.A.*, 1943, *123*:755.
14. Bumpus, H. C., Jr. Carcinoma of the prostate; a clinical study of 1000 cases, *Surg., Gynec. & Obst.*, 1926, *43*:150.
15. Kahle, P. J., Ogden, H. D., Jr. and Getzoff, P. L. The effect of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of the prostate gland, clinical observations, *J. Urol.*, 1942, *48*:83.
    Kahle, P J., Schenken, J. R. and Burns, E. L. Clinical and pathologic effects of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of the prostate gland, a continuing study, *ibid.*, 1943, *50*:711.
16. Vallett, B. S. Radical perineal prostatectomy subsequent to bilateral orchiectomy, *Delaware State M. J.*, 1944, *16*:19.
17. Parlow, A. L. Advanced cancer of the prostate, *New York State J. Med.*, 1945, *45*:383.

(Discussion on "The Role of Bilateral Orchiectomy in the Treatment of Carcinoma of the Prostate Gland" by Drs. Scott and Benjamin follows on next page.)

Discussion by DR. JOHN S. HESLIN: (by invitation)

I want to express my appreciation for the invitation to open the discussion of Dr. Scott's paper. His presentation is a valuable contribution at this time, and after reviewing a survey of our cases I can well appreciate the great amount of work his complete study has meant.

A review of our cases of carcinoma of the prostate in the Albany Hospital shows our experience to be similar to that of others who have reported their results. A bilateral orchiectomy with resection was routine procedure until recently and gives us a fair number of cases upon which to evaluate results.

The excellent results obtained in our early cases led to great enthusiasm, only to be followed by uncertainty as unrelieved cases and recurrences appeared. This survey tends to restore some of our confidence in the procedure as a valuable palliative measure in this serious disease. Recently we have performed orchiectomy only in the presence of definite pain due to metastases, or x-ray evidence of metastases, or an elevation of acid serum phosphatase.

An incidence of 15 per cent malignancy was revealed in our series of 376 cases undergoing transurethral resection this past year.

For this survey 96 cases of carcinoma of the prostate upon which orchiectomy was performed, between July 1, 1941 and September 1944, were reviewed by questionnaire and personal examination. Twenty-eight or 34.4 per cent were reported as having died; 21 failed to reply; 15 answered the questionnaire, and 32 appeared for examination. The following observations were made from this material.

The effect of orchiectomy upon acid serum phosphatase studies in 21 Cases

16	Decreased	76.1%
4	Elevated	19.2%
1	No change	

The relation of x-ray evidence of metastases and acid serum phosphatase

X-ray positive for metastases	32 cases	
Elevated acid serum phosphatase	22 cases	68.75%
Decreased acid serum phosphatase	10 cases	31.25%

Effect of orchiectomy upon pain due to metastases (47 cases)

Yrs. Since Operation	*Number of Cases*	*Pain Present Before Operation*	*Pain Relieved By Operation*	*Pain Recurred To Date*
3	1	1	0	
2½	6	4	3	0
2	16	10	8	2
1½	9	7	7	3
1	15	9	7	2
	47	31 (65.9%)	25 (80.6%)	7 (28%)

Acid serum phosphatase was elevated in all cases of recurrence of pain.

Effect of orchiectomy upon the prostate gland (32 cases examined by palpation)

No evidence of malignancy	14	43.75%
Suspicious of malignancy	10	31.25%
Malignant	8	25%

As a result of this survey, we were impressed by the following:

1. Number of glands with no evidence of malignancy upon rectal palpation (43.75 per cent of 32 cases examined).

2. 80.6 per cent of 31 cases were relieved of pain, with a small number of recurrences.

3. The excellent bladder function and general health in the great majority of patients

We are convinced that in this procedure we have a valuable palliative measure in the control of pain from the metastases of carcinoma of the prostate. Its value as a prophylactic measure, the stage in which it will give maximum results and its relation to stilbestrol therapy must await further clinical and biological studies.

Discussion by DR. HENRY G. BUGBEE:

Only through such papers as Dr. Scott's will we be able to properly evaluate the role of orchiectomy in the treatment of cancer of the prostate. It is to be expected that those of us who have practiced urology for a considerable period of time will view any innovation in the man-

agement of this perennial problem with reserve and even a certain amount of cynicism. However, when one ceases to be open minded, his judgment becomes biased and he limits his sphere of usefulness to the patient.

Through the years many of us have at one time or another employed almost every method of treatment or operation, in an attempt to cure this disease. In some instances the results of treatment have been more distressing than the disease itself, such as the toxemia resulting from various methods of radiation and the mutilation often incident to efforts at surgical removal of the growth, or even of palliative surgery. Furthermore, we have noted a great variation in the course of the disease when untreated. The cancer in many instances is slow in its growth, such patients often living for years in comparative comfort. This leads us to interpret the occasional glowing accounts of a favorable course following operation or radiation as instances of a slowly growing type of cancer, cases that might have done well under any type of treatment or no treatment at all. Only through the treatment of a large number of cases and observations over a period of from five to ten years can one correctly evaluate any method of treatment for cancer of the prostate.

It is now some years since Huggins presented his studies, and most of us have treated a sufficient number of cases to have formed some fairly definite ideas regarding the efficacy of orchiectomy in the management of prostatic carcinoma. The striking and immediate improvement that has often been noted, especially in far advanced and disseminated cancer, gave promise of what some thought might prove to be a cure for this most difficult of urologic problems. However, sufficient time has elapsed and the number of cases so treated has mounted, so that I very much doubt if any urologist is willing to believe that orchiectomy can ever be considered a cure for cancer of the prostate. If, however, it does no more than give a temporary relief from pain, reduce the size of the prostate, soften the gland and improve the general wellbeing of the patient, as it does in so many instances, it has added much to our means of treating this distressing condition.

My own experience, observations of cases of other urologists and reviews of clinical reports, lead me to believe that the benefit derived from orchiectomy is temporary and is a procedure to be held in reserve until it is required to bring about the relief that we can usually expect,

namely relief of local pain from pressure or incident to metastasis, and to raise the general morale of the patient. If this operation is carried out early in the disease, the relief that it affords at a later period, when it is most needed, is denied the patient. I very much doubt if orchiectomy will reduce urinary retention, a phenomenon that has been noted following radiation.

The studies that have been carried out in blood chemistry associated with cancer of the prostate and the changes that have been recorded following orchiectomy are most interesting and give us corroborative evidence of the course of this disease, but from my own experience, such data would seldom provide an indication for orchiectomy.

Much has been written of late regarding total or radical prostatectomy for the cure of cancer of the prostate. If one encountered such a growth in a very early stage and it was so localized in the gland that a removal of gland and capsule would eliminate the cancer, such an operation would be ideal. The most favorable cases that I have encountered were those in which a small area of cancer was found on pathological section in prostates removed for hypertrophy and in which cancer was not suspected before operation. Eight such cases were reported in 1928. One subsequently died of cardiovascular disease, the others of cancer with definite local extension of the growth. I have seen perineal prostatectomy carried out by some of our most able surgeons for supposed cancer of the prostate and the hard nodule suspected of malignancy proved to be benign; I have seen also a prostate exposed, a suspected nodule excised, sectioned, found to be benign and the perineum closed. These procedures carried out by our most ardent advocates of this type of operative relief, make me wonder how often we really are able to select those cases most favorable for this type of operation. The various series showing results of radical operation that I have seen exhibited have not impressed me favorably from the standpoint of operative mortality, functional results and length of life, even though the operations were performed by our most skilful perineal surgeons. To my mind their results do not compare favorably with the symptomatic relief obtained through the elimination of retention by transurethral resection and the employment of orchiectomy to alleviate the pain, local and general, due to metastasis late in the disease.

A patient now 84 years of age who has been under my care since 1918, at which time he had an unmistakable cancer of the prostate,

went on comfortably until 5 years ago when he developed retention. Transurethral resection gave relief and he now attends daily to an active law practice, voids once at night, every 4 or 5 hours during the day and says he is comfortable. I still have orchiectomy to offer him when the symptoms warrant. I could cite other cases that have been observed over shorter but appreciable periods of time, in which the growth has progressed slowly. Sulfa drugs have played an important role in controlling infection and stilbestrol has occasionally served as a valuable adjunct.

These brief remarks are not intended as a deterrent toward any one method of treatment of cancer of the prostate, but from the facts at hand I do not believe that we are yet in a position to talk about cures in this disease. This does not mean that we should not make every effort to detect those cases which might be cured, especially through an attempted complete removal. Rarely such cases may be encountered. In recording such a result, however, one cannot lose sight of the cases which have often shown little change over a long period of years and wonder if the case reported might not have been such a type of growth. The advisability of attempting prostatectomy following orchiectomy can only be evaluated following its trial in a series of cases, observed over a sufficient length of time.

At the present time I believe that we should give these cases the benefit of what we think will give the individual the greatest relief over the longest period of time, and in this role orchiectomy has established a very definite place.

Dr. Scott has given us a clear, comprehensive, unbiased report of his wide experience with this operation. His remarks will add considerably to our knowledge and we are indebted to him for them.

Discussion by DR. OSWALD S. LOWSLEY:

I enjoyed Dr. Scott's paper very much. We all know that cancer is the black page in all phases of medical practice. The etiology of prostatic carcinoma is unknown, but our observations lead us to believe that Huggins and Munger are on the right track when they state that there is a relationship of the androgenic hormone to this type of cancer. Yet as time elapses, we find that while castration is very helpful in many cases, it is not the complete answer to the cancer problem.

In our department at New York Hospital we try, in all controversial

matters, to give each member of the department leeway to do what he thinks best. Thus we have one group which has done castration on every case of cancer of the prostrate, another which has done it only when pain develops, and so forth. A great mass of statistics is necessary to arrive at characteristic findings, even though it may seem quite confusing at times. So far, the number of our cases is not sufficient for definite conclusions. However, Dr. Pavlow, our resident, has gathered together some statistics on 276 patients who have come under our care. From these we have made certain observations, briefly as follows:

1. Prostatic carcinoma seems to be of two types. The large majority (over 75 per cent) begin in the posterior lobe. The remainder are found in adenomatous hypertrophies which have been removed, their presence being unsuspected until revealed by the microscope. A morphologic peculiarity of these cancers is the diversity of their forms. Adenocarcinoma is the commonest type, but scirrhus, medullary, and squamous cell carcinoma may be found, sometimes in the same specimen. The frequency of metastases to the pelvic bones and the lumbar vertebrae is well known. However, dissemination may also occur in distant areas.

2. These cancers not infrequently occur in men who are under the age usually associated with benign hypertrophy, that is, 50 years and over. Of our 276 patients, the youngest was 45 years and 4 others were under 50 years of age. The greatest incidence (42 per cent) was in the sixth decade.

3. The symptoms of prostatic carcinoma occur late and are not easily differentiated from those of adenomatous hypertrophy. Over 50 per cent of our patients had symptoms less than one year. Urinary disturbances, usually the first symptoms, were present in all but 12 of our cases. Pain, which often is due to skeletal metastases, was present in 63 cases, hematuria in 61, and loss of weight in 34. These are all late manifestations and not helpful in diagnosing the condition early. Four patients with quite extensive carcinomas had no symptoms whatsoever, their tumors being discovered during physical examinations for other reasons.

4. Over one-half (56 per cent) of our cases were diagnosed by rectal palpation. In doubtful cases, microscopic examination of tissue removed from suspicious areas with a biopsy instrument introduced through the perineum successfully establishes the diagnosis as a rule.

Carcinomas coexisting with adenomatous hypertrophy may be very difficult to diagnose clinically.

5. We have found acid serum phosphatase studies very helpful in determining the presence of skeletal metastases, and as an index to the progression of metastases. In cases having 10 or more King and Armstrong units per 100 cc. of blood, definite x-ray evidence of such metastasis either is present or is likely to develop subsequently.

6. The prognosis of prostatic carcinoma is grave. In early tumors which have not extended beyond the prostate and its capsule, radical removal of the prostate and seminal vesicles, plus castration by the method described above, would seem to offer the best hope of a cure of the disease. In cases where the growth has extended beyond the limits of the prostate, total prostatectomy without the removal of the seminal vesicles, plus castration, will usually relieve the patient's symptoms and prevent recurrence of the disease at the bladder neck, and thus the patient will not die of the effects of urinary obstruction. Stilbestrol is helpful when castration is not permitted.

7. Regarding treatment, it is difficult to summarize these statistics, but the following is clear:

From 1921 to 1938, a period of 17 years, various forms of treatment were utilized, for the most part open operation and implantation of radon seeds, often with supplementary deep x-ray therapy. Eighteen out of the 165 patients are known to have lived 3 years or longer, one hardy soul being alive 8 years after a transurethral resection with radon implantation and deep x-ray therapy.

From January 1938 to January 1944 there was a total of 111 cases: 64 without castration and 47 with castration. Of the former, 44 patients with prostatectomy or resection were followed up. Thirteen of these lived 3 years or longer, all after open operations. The longest survival was 5½ years. This patient is still alive and quite well.

Of the 47 patients who had castration, 20 were alive on January 1, 1944: 8 after open operation and castration, 16 after transurethral resection and castration, and one after castration only. One cannot draw definite conclusions regarding improvement in the mortality rate of the castrated cases as compared with the non-castrated cases because insufficient time (only 3½ years) has elapsed since this method was instituted.

In our experience the procedure has not made very much difference

in the sexual powers, perhaps because most of these patients are beyond the age of sexual activity. Eunuchs in the Far East have been known to retain their sexual vigor for many years after castration.

There is no doubt but that the castrated patients show a prompt and often complete freedom from pain, gain weight, and have a feeling and appearance of well-being. This last is heightened by the splendid cosmetic effect produced by the implantation of fat into the tunica albuginea after removal of the testicular tissue as described above. Even should it turn out, as it well may, that life is not remarkably extended by the addition of castration to our armamentarium, this procedure is still worth while, because it is our duty as physicians not only to preserve life but to relieve suffering, and castration in carcinoma of the prostate unquestionably does that.

Again may I say that I appreciate Dr. Scott's paper. It is a very accurate statistical study, and we are indeed fortunate to have had it presented to us.

Discussion by DR. ARCHIE L. DEAN:

After reading Dr. Scott's excellent paper and having had the opportunity of hearing him present it, one must praise his work because it consists of a sizable number of patients carefully studied. The men studied were apparently in about the usual condition of patients commonly seen with prostatic cancers, and responded to the treatment he gave them in about the same way that other similar groups have reacted to the most careful endocrine treatment. The only points of Dr. Scott's work which are not quite clear to me are—

1. When, in addition to orchiectomy, did he employ stilbestrol?
2. Why did he use this drug, and
3. In what way did stilbestrol, superimposed on castration, modify the patient's clinical course?

At Memorial Hospital we have been able to treat and observe over reasonably long periods 120 patients with histologically proved prostatic cancers. Additional patients were treated but, for various reasons, they were unsatisfactory for close study. On the basis of our experiences and the work of others there appears to be a close similarity in the clinical picture presented by every comprehensive series of patients with prostatic cancers treated by modification of the endocrines. This makes the work of all reporting urologists more convincing.

On the basis of their response to treatment we recognize, in a rough way, three groups of patients:

Group I. There is a small minority of men who, in spite of all treatment, follow an uninterrupted downhill course ending in death.

Group II. The great majority are benefitted. Speaking generally and somewhat optimistically, pain is relieved promptly and completely, appetites are much improved, physical and mental ability is reestablished, the primary tumor softens and shrinks, and metastases in soft parts, including even large secondary deposits in the lungs, disappear until all in all a remarkably favorable transformation has taken place. After a varying period of good health (between 7 and 9 months in our patients) the majority, about 60 per cent, relapse and the disease progresses at a rate apparently more rapid than before treatment was first given, until death occurs. We have been unable to significantly alter this fatal outcome by administering stilbestrol to castrated patients or by castrating those men treated primarily with stilbestrol.

Group III. The remaining patients who survive the period of common relapse may continue indefinitely longer in seemingly good health but in one by one the prostatic cancers appear to become reactive and they succumb. During this period it is also possible, as Dr. Scott stated, for patients to die of intercurrent disease. There may be a few individuals who continue well. A small number of our patients show no disease, excepting perhaps long unchanged x-ray evidence of bone metastases, for more than 3 years after treatment was started. One does not know as yet what their future development will be.

When we first began to treat cancers of the prostate by modification of the endocrines, alternate patients were treated by castration and by the administration of stilbestrol. After observing the results on nearly 80 patients the administration of stilbestrol, 1 mg. daily by mouth at bed time, became and has remained the primary treatment of choice, Comparison of these two types of treatment in our hands shows that castration often produces a spectacular disappearance of bone pain in 24 to 48 hours whereas 1 mg. daily of stilbestrol requires 7 to 14 days to bring about this result, although large initial doses of estrogens in the form of pellets may equal the immediate effects of castration. Other than this we have observed no feature of the disease which was not as greatly improved by the drug as by operation, nor have we found reason to combine the two treatments.

Because Dr. Woodward, physiological chemist of the Memorial Hospital, was one of the pioneers in demonstrating the significance of the phosphatases in cancers of the prostate and in other diseases, we have for years supplemented clinical observations on patients with prostatic cancers with frequent assays of the acid and alkaline phosphatases of the serum and have become convinced of their diagnostic and prognostic value. Although there is little clinical difference between the prostatic cancers of castrated patients and those treated with stilbestrol, phosphates studies suggest that the results are brought about by different processes. After castration the acid phosphatase quickly drops to normal or nearly normal. When bone metastases are present, the alkaline phosphatase at first increases in 66 per cent of the patients. After about 2 months it decreases to far below the initial reading. This suggests that during endocrine rearrangement following castration there is some change which stimulates bone regeneration. Since alkaline phosphatase rises after castration in other diseases with bone metastases, we believe this reaction is a bone reaction rather than a prostatic cancer reaction; in other words, it is a reaction of the bone around the tumor rather than a reaction of the cancer metastasis in the bone.

When stilbestrol is administered the serum acid phosphatase decreases to normal or toward normal, but not so rapidly as after castration. In the presence of bone metastases there is an initial rise of alkaline phosphatase in only 20 per cent of cases. This is followed by a gradual fall.

In general, phosphatase studies suggest that after either castration or stilbestrol there is a change in the metabolism of the prostatic cancer characterized by a diminution of the acid phosphatase.

We have experienced difficulty in recognizing x-ray evidence of changes in bone metastases during and after treatment. Since the pictures we have seen have changed slowly, if at all, we depend exclusively on measurements of the serum alkaline phosphatase to show the immediate status of bone lesions. This test appears to be quite sensitive for the purpose.

From the fact that there is general agreement concerning the clinical response of prostatic cancers to endocrine treatment it would appear that urologists have well performed their functions of administering the best treatment known and observing its effects accurately. Even so, unfortunately, the treatment of this important disease remains em-

pirical because one does not know how to choose the most effective treatment for the individual patient nor can one accurately predict his response. I believe the answers to these and many other questions of equal importance will be solved by steroid chemists after they succeed in isolating the different androgens and estrogens and learning the physiological functions which each performs.

Discussion by DR. E. GRANVILLE CRABTREE:

It has been a great pleasure to be present as a guest of the Society this evening. I have enjoyed Dr. Scott's paper very much indeed. It has a definite place in the long series of attempts which are being made throughout the country to establish an exact basis for applying the important contribution of Huggins for the treatment of cancer of the prostate for the best interest of the patient. It has not been easy to arrive at that end.

Progress towards this end has been delayed by unfortunate lay publicity which is so freely given in medical matters nowadays, such as the publication by DeKreif on this subject some time ago. The unwarranted optimism there expressed is not now borne out by present facts. It has been necessary for urologists, from that time on, to combat (often unsuccessfully) the patient's conviction that the endocrines are curative. I have also attempted to influence patients to permit total prostatectomy after apparent disappearance of cancer under hormonal therapy, only to find that articles in the lay press stood in my way. Dr. Scott's incidents of similar nature indicate that I have not been alone in this. Not one of my patients would consent to operation, which might have been curative, in the stage of improvement. The lay press assumes, perhaps unconsciously, the role of advisors without responsibility—a dangerous situation in any field.

I shall watch with interest developments which follow the recent story of the Smithwick operation in *The Saturday Evening Post*. This new and as yet not fully established procedure is now similarly placed in this subject of prostatic cancer. The surgery for the condition is difficult and few adequately trained surgeons capable of the operation exist at the time wide publicity creates wide demand.

I wish the lay press would allow us time to establish more nearly the value of new procedures before they rush publicity which is capable of doing great harm.

Discussion by DR. CLYDE L. DEMING:

Dr. Scott's paper has been extremely interesting, and I appreciate the honor of being asked to discuss it. I shall confine myself to just a word of comment.

Briefly, we accept three main facts in the consideration of the results of hormonal therapy for cancer of the prostate: (1) Pain is relieved in 80 per cent of cases in which there are metastases. (2) About 60 per cent are improved as far as general wellbeing of the patient is concerned. (3) As far as we know, no case has ever been cured by hormonal therapy alone. That leaves us with the necessity of doing a radical extirpation of the prostate in those cases where the tumor is limited to the prostatic capsule.

The future approach to this problem lies along two avenues. First, there is that of clinical study on the part of the urologist. He must find out when and how much of the hormone to give. The second point may be a far-fetched idea, but I believe that it lies just ahead of us; that is, to give hormonal therapy as a prophylactic so that no one will develop a prostatic cancer. This latter avenue must be approached through the biochemist. He must first tell us what the carcinogenic agent in the testis is which causes a stimulation of the epithelium of the prostate to grow into a cancerous condition. He must also find out, if possible, what anti-carcinogenic is present in stilbestrol or similar substances.

Dr. Scott has made an approach to these problems clinically. He is attempting to give us a procedure which will make an inoperable case an operable one. First, he reduces the cancerous growth, then removes it in those cases in which it seems indicated. Certainly one should not attempt a total removal of the prostate if there is an elevation of the acid serum phosphatase.

In support of Dr. Scott's contention that if it is possible to reduce the size of the prostate by hormonal therapy, surgical removal should then be advocated, I would like to remind you of a case reported by Dr. Herbst of Washington. It is only a single case, but a very interesting one. The case was one of an undoubted carcinoma of the prostate proved by biopsy. While extensive hormonal therapy left the glandular tissue greatly reduced, even to normal size, soft and elastic to palpation, yet after the patient's death from coronary disease or pneumonia (I forget which) autopsy showed in the center of the prostate a small nest of visible cancer cells.

DR. SCOTT: (Closing)

First I want to thank Dr. Delzell and the members of the New York Society of the American Urological Association for the privilege of presenting this paper, in which Dr. Benjamin joins me. Also we greatly appreciate the courtesy and consideration shown us by those who have discussed the paper.

We agree with Dr. Bugbee that because it is seldom possible to determine in advance with any degree of accuracy the course of a patient with carcinoma of the prostate gland it is difficult to decide upon the type of therapy to use and to evaluate properly its effect. In our series, 60 per cent of the patients with the predominantly undifferentiated type of carcinoma of the prostate and 26.7 per cent with the predominantly adenocarcinoma type of tumor were dead when this series was completed. A histological study of tissue from the prostate might give some information as to the prognosis of the patient and the type of therapy that would be of most value. It would seem that Dr. Bugbee's evaluation of the radical prostatectomy in the treatment of carcinoma of the prostate is definitely different than ours. It is only by such honest difference of opinion that truths are determined and medical progress is made.

We agree with Dr. Lowsley concerning his uncertainty with reference to the relative merits of orchiectomy and estrogenic therapy. We are of the opinion that in certain cases where the response to one type of therapy was not quite satisfactory the supplementary use of the other sometimes proved to be quite beneficial. In one of our cases in which the effect of orchiectomy was not sufficient to permit a radical follow-up prostatectomy, the supplementary use of stilbestrol made this procedure possible.

In answer to Dr. Dean's query as to the factors that aid us in making a choice between orchiectomy and stilbestrol therapy we can only state that we are governed by no set rules in this respect but rather by the findings in each case. For example, one of our patients who had a history of a coronary thrombosis three months previously had an involvement of the prostate, when first seen, that seemed a little too extensive to permit its complete removal without preliminary shrinkage. Because of his cardiac history and the findings it seemed advisable, if possible, to prepare him with stilbestrol therapy. His response

to this treatment was so satisfactory that it was possible to perform a follow-up radical prostatectomy. In such cases, where a moderate decrease in the size of the prostate gland will permit a radical prostatectomy it is probably wise to try stilbestrol therapy first. We are of the opinion that if we had used stilbestrol therapy in preference to orchiectomy in the patient who refused to have "any more cutting" he might have consented to a follow-up radical prostatectomy.

The results obtained by Dr. Heslin in the very excellent review of his cases of carcinoma of the prostate gland treated by orchiectomy confirm the results obtained by us and others by this therapy.

It is much too soon to know what will happen to these patients who have had a follow-up radical prostatectomy after preliminary bilateral orchiectomy or stilbestrol therapy, but we hope the results will be an improvement over those obtained by orchiectomy or stilbestrol therapy alone or in combination. It is our intention to try this combined therapy upon a series of patients and it is our hope that others will do the same and report their results.

RECENT ACCESSIONS TO THE LIBRARY

("Possession does not imply approval.")

American Academy of Orthopaedic Surgeons. *The American Academy of Orthopaedic Surgeons presents lectures on reconstruction surgery.* [Ann Arbor, Edwards], 1944, 568 p.

American Society for the Control of Cancer. New York City Cancer Committee. *History of the American Society for the Control of Cancer, 1913-1943.* [N. Y., New York City Cancer Committee, 1944], 38 leaves.

Appleton, J. L. T. *Bacterial infection, with special reference to dental practice.* Phil., Lea, [1944], 498 p.

Atkins, H. J. B. *After-treatment.* 2. ed. Oxford, Blackwell, 1944, 311 p.

Babkin, B. P. *Secretory mechanism of the digestive glands.* N. Y., Hoeber, [1944], 900 p.

Barclay, A. E.; Franklin, K. J. & Prichard, M. M. L. *The foetal circulation.* Oxford, Blackwell, 1944, 275 p.

Binger, C. A. L. *The doctor's job.* N. Y., Norton, [1945], 243 p.

Boas, E. P. *Treatment of the patient past fifty.* [2. ed.] Chic., Year Book Publishers, [1944], 414 p.

Briggs, I. G. *They gave me a crown; the diversions of a doctor in war and peace.* London, Jenkins, [1944], 220 p.

Broster, L. R. *Endocrine man; a study in the surgery of sex.* London, Heinemann, 1944, 144 p.

Celestino da Costa, A. P. & Chaves, P. R. da S. *Tratado elementar de histologia e anatomia micróscopica.* Lisboa, Livraria Luso-Espanhola, [1944], 2 v. in 3.

Conference on Convalescence and Rehabilitation, New York, 1944. *Convalescence and rehabilitation; proceedings of the Conference held under the auspices of the Committee on Public Health Relation of The New York Academy of Medicine.* N. Y., Committee on Pub. Health Relations, N. Y. Acad. of Med., [1945], 223 p.

Cooley, R. A. & Kohls, G. M. *The Argasidae of North America, Central America and Cuba.* Notre Dame, Ind., Univ. Press, 1944, 152 p.

Corner, G. W. *Ourselves unborn; an embryologist's essay on man.* New Haven, Yale Univ. Press, [1945], 188 p.

Craig, C. F. *The etiology, diagnosis, and treatment of amebiasis.* Balt., Williams, 1944, 332 p.

Criep, L. H. *Essentials of allergy.* Phil., Lippincott, [1945], 381 p.

Davison, W. C. *The compleat pediatrician.* 4. ed. Durham, N. C., Duke Univ. Press, 1944, 256 sections.

Dentist (The) and his patient, by D. Friend [and others]. N. Y., Revere, 1944, 480 p.

Diagnosis (The) and treatment of cardiovascular disease, edited by W. D. Stroud. 3. ed. Phil., Davis, 1945, 2 v.

Ellis, R. G. *The classification and treatment of injuries to the teeth of children.* Chic., Year Book Publishers, [1945], 248 p.

Farm Foundation. *Medical care and health services for rural people.* Chic., Farm Foundation, [1944], 226 p.

Fordham, M. S. M. *The life of childhood; a contribution to analytical psychology.* London, Paul, [1944], 154 p.

Garry, T. G. *The prevention and treatment of disease in warm climates.* [London], Medical Publications, [1944], 94 p.

Girgolav, S. S.; Levit, V. S. [and others]. *Uchebnik chastnoy khirurgii. [Textbook of special surgery].* Moskva, MEDGIZ, 1944, 2 v.

Gunn, J. A. *An introduction to pharmacology and therapeutics.* 7. ed. London, Milford, 1944, 268 p.

Haas, L. J. *Practical occupational therapy for the mentally and nervously ill.* Milwaukee, Bruce, [1944], 432 p.

Harries, E. H. R. & Mitman, M. *Clinical practice in infectious diseases.* 2. ed. Edinburgh, Livingstone, 1944, 570 p.

Harris, I. *The woof of life.* London, Longmans, [1944], 113 p.

Haymaker, W. & Woodhall, M. B. *Peripheral nerve injuries.* Phil., Saunders, 1945, 227 p.

Hotchkiss, R. S. *Fertility in men.* Phil., Lippincott, [1944], 216 p.

Janney, J. C. *Medical gynecology.* Phil., Saunders, 1945, 389 p.

Jones, F. W. *Structure and function as seen in the foot.* London, Baillière, 1944, 329 p.

Kisch, B. Z., ed. *Harry Koster, M. D., March 18, 1893—June 2, 1943.* N. Y., Brooklyn Med. Press, [1944], 103 p.

Kohn, L. W. *Your digestive system.* Phil., Blakiston, [1944], 274 p.

Kolmer, J. A. & Boerner, F. *Approved laboratory technic.* 4. ed. N. Y., Appleton-Century, [1945], 1017 p.

Landsteiner, K. *The specificity of serological reactions.* Rev. ed. Cambridge, Mass., Harvard Univ. Press, 1945, 310 p.

Lawson, F. D. *The human voice.* N. Y., Harper, [1944], 94 p.

Layton, T. B. *An industry of health, being an exposition of 'Assumption B' [of the Beveridge report].* 2. ed. London, Heinemann, 1944, 100 p.

Lessa, A. *Dadores se sangue.* Lisboa, Livraria Luso-Espanhola, 1944, 516 p.

Levy, H. *National health insurance; a critical study.* Cambridge, [Eng.], Univ. Press, 1944, 366 p.

Luckiesh, M. *Light, vision and seeing.* N. Y., Van Nostrand, [1944], 323 p.

Lull, C. B. & Hingson, R. A. *Control of pain in childbirth.* Phil., Lippincott, [1944], 356 p.

Lyle, D. J. *Neuro-ophthalmology.* Springfield, Ill., Thomas, 1945, 395 p.

McCarrison, (Sir) R. *Nutrition and national health.* London, Faber, [1944], 75 p.

McCrea, L. E. *Clinical cystoscopy.* Phil., Davis, 1945, 2 v.

McDowall, R. J. S. *Sane psychology; a biological introduction to psychology.* London, Murray, [1944], 275 p.

Mackie, T. T.; Hunter, G. W. & Worth, C. B. *A manual of tropical medicine.* Phil., Saunders, 1945, 727 p.

McLachlan, A. E. W. *Handbook of diagnosis & treatment of venereal diseases.* Edinburgh, Livingstone, 1944, 364 p.

McMillan, D. *Obstetric cases.* 1. series. Christchurch, N. Z., Peryer, 1943, 141 p.

MacQuarrie, A. W. *Casualty work for advanced first-aid students.* Edinburgh, Livingstone, 1944, 231 p.

Manchée, D. *Social service in a general hospital.* London, Baillière, 1944, 164 p.

Matheson, R. *Handbook of the mosquitoes of North America.* 2. ed. Ithaca, Comstock, 1944, 314 p.

Mel'nikov, A. V. *Klinika septicheskikh oslojneniy ognestrl'nykh ran.* [*Clinic of septic complications of gunshot wounds.*] Moskva, MEDGIZ, 1943, 178 p.

Nissen, R. *Duodenal and jejunal peptic ulcer; technic of resection.* N. Y., Grune, 1945, 143 p.

Oldfield, J. *Healing and the conquest of pain.* London, Rider, [1944], 112 p.

Outline of the amino acids and proteins, edited by M. Sahyun. N. Y., Reinhold, 1944, 251 p.

Page, I. H. & Corcoran, A. C. *Arterial hypertension.* Chic., Year Book Publishers, [1945], 352 p.

Phelps, E. B. *Stream sanitation.* N. Y., Wiley, [1944], 276 p.

Pomeranz, H. *Your respiratory system.* Phil., Blakiston, [1944], 298 p.

dos Santos, J. C. *Patologia geral das isquémis dos membros.* Lisboa, Livraria Luso-Espanhola, 1944, 264 p.

Scherf, D. & Boyd, L. J. *Clinical electrocardiography.* 2. ed. London, Heinemann, 1945, 403 p.

Siegler, S. L. *Fertility in women.* Phil., Lippincott, [1944], 450 p.

Sokoloff, B. F. *The civilized diseases: you can cure them.* [N. Y.], Howell, [1944], 309 p.

Therapeutics of infancy and childhood, edited by H. R. Litchfield and L. R. Dembo. 2. ed. Phil., Davis, 1945, vol. 1 & 2.

Truax, R. *Joseph Lister.* Indianapolis, Bobbs-Merrill, [1944], 287 p.

Unger, L. *Bronchial asthma.* Springfield, Ill., Thomas, 1945, 724 p.